we feel that NALT patients also should receive PEG-IFN α plus RBV treatment if liver fibrosis is not advanced.

Further, our data demonstrated that total cholesterol could be useful for predicting which NALT patients will achieve SVR. These results showed that the total cholesterol level is inversely associated with liver fiborosis.[30,31] Therefore, serum total cholesterol might be helpful for a determination to treat NALT patients with PEG-IFN α-2b plus RBV, whether or not liver fibrosis is advanced, even when we cannot do liver biopsy. We feel that whether or not to initiate therapy should be decided not only by age and serum ALT level, but also by serum total cholesterol and the guidelines of AASLD as above mentioned.[12]

Although IFN α treatment for patients with NALT has been reported to cause ALT-flare ups after treatment,[32,33] we previously reported that the number of patients with elevated ALT levels in a 2-year follow up was not significantly different between patients treated with IFN α and untreated patients.[34] There has been only one report that PEG-IFN α-2a plus RBV combination treatment did not cause ALT flare-ups after treatment,[16] but the precise relationship remains to be elucidated. Our data indicated that the ALT flare up rate after treatment was 15.8%, and watching non-SVR patients carefully after treatment is important to check for ALT flare ups. Along with a report that over 60% of patients with NALT have an elevated ALT level at 3 years,[35] we considered that the PEG-IFN α plus RBV combination treatment is also safe for patients with NALT, although we must note that we did not follow up a full 2 years to observe the change of ALT levels.

This study has a limitation that liver biopsy was done only for about half of the enrolled patients and that we could not measure biomarkers of liver fibrosis such as hyaluronic acid, so we could not precisely estimate the liver fibrosis. However, because the present study was a large multicenter design, the findings are of great interest for clarifying the efficacy and safety of PEG-IFN α-2b plus RBV combination treatment for patients with NALT.

CONCLUSIONS

THE EFFICACY AND safety of PEG-IFN α-2b plus RBV combination therapy for patients with chronic HCV infection who have NALT is similar to that of patients with elevated ALT levels. These results indicate that patients with NALT are suitable candidates for treatment with PEG-IFN α-2b plus RBV.

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REFERENCES

1 Hayashi J, Furusyo N, Ariyama I, Sawayama Y, Etoh Y, Kashiwagi S. A relationship between the evaluation of hepatitis C virus variants, liver damage, and hepatocellular carcinoma in patients. *J Infect Dis* 2000; **181**: 1523–7.
2 Hayashi J, Ohmiya M, Kishihara Y *et al.* A statistical analysis of predictive factors of response to human lymphoblastoid interferon in patients with chronic hepatitis C. *Am J Gastroenterol* 1994; **89**: 2151–6.
3 Furusyo N, Hayashi J, Ohmiya M *et al.* Differences between interferon-alpha and–beta treatment for patients with chronic hepatitis C virus infection. *Dig Dis Sci* 1999; **44**: 608–17.
4 Furusyo N, Hayashi J, Ueno K *et al.* Human lymphoblastoid interferon treatment for patients with hepatitis C virus-related cirrhosis. *Clin Ther* 1997; **19**: 1352–67.
5 Kashiwagi K, Furusyo N, Kubo N *et al.* A prospective comparison of the effect of interferon-alpha and interferon-beta treatment in patients with chronic hepatitis C on the incidence of hepatocellular carcinoma development. *J Infect Chemother* 2003; **9**: 333–40.
6 Hayashi J, Kishihara Y, Yamaji K *et al.* Hepatitis C viral quasispecies and liver damage in patients with chronic hepatitis C viral infection. *Hepatology* 1997; **25**: 697–701.
7 Shiffman ML, Diago M, Tran A *et al.* Chronic hepatitis C in patients with persistently normal alanine transaminase levels. *Clin Gastroenterol Hepatol* 2006; **4**: 645–52.
8 Prati D, Taioli E, Zanella A *et al.* Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002; **137**: 1–10.
9 Alberti A, Noventa F, Benvegnu L, Boccato S, Gatta A. Prevalence of liver disease in a population of asymptomatic persons with hepatitis C virus infection. *Ann Intern Med* 2002; **137**: 961–4.
10 Tassopoulos NC. Treatment in patients with normal ALT levels. EASL International Consensus Conference on Hepatitis C: Consensus Statement. *J Hepatol* 1999; **30**: 956–61.
11 Marcellin P, Levy S, Erlinger S. Therapy of hepatitis C: patients with normal aminotransferase levels. National Institutes of Health Consensus Development Conference Panel Statement: Management of Hepatitis C. *Hepatology* 1997; **26**: 133S–6S.
12 Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335–74.

13 Puoti C, Castellacci R, Montagnese F *et al.* Histological and virological features and follow-up of hepatitis C virus carriers with normal aminotransferase levels: the Italian prospective study of the asymptomatic C carriers (ISACC). *J Hepatol* 2002; **37**: 117–23.
14 Alberti A, Noventa F, Benvegnù L, Boccato S, Gatta A. Prevalence of liver disease in a population of asymptomatic persons with hepatitis C virus infection. *Ann Intern Med* 2002; **137**: 961–4.
15 Puoti C, Magrini A, Stati T *et al.* Clinical, histological, and virological features of hepatitis C virus carriers with persistently normal or abnormal alanine transaminase levels. *Hepatology* 1997; 26: 1393–8.
16 Zeuzem S, Diago M, Gane E *et al.* Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology* 2004; **127**: 1724–32.
17 Puoti C, Pellicelli AM, Romano M *et al.* Treatment of hepatitis C virus carriers with persistently normal alanine aminotransferase levels with peginterferon alpha-2a and ribavirin: a multicentric study. *Liver Int* 2009; **29**: 1479–84.
18 Deuffic-Burban S, Babany G, Lonjon-Domanec I *et al.* Impact of pegylated interferon and ribavirin on morbidity and mortality in patients with chronic hepatitis C and normal aminotransferases in France. *Hepatology* 2009; **50**: 1351–9.
19 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975–82.
20 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358: 958–65.
21 Pattullo V, Heathcote EJ, Wong DK. Superior response to pegylated interferon and ribavirin in Asians with chronic hepatitis C. *Hepatol Int* 2010; 4: 723–31.
22 Furusyo N, Katoh M, Tanabe Y *et al.* Interferon alpha plus ribavirin combination treatment of Japanese chronic hepatitis C patients with HCV genotype 2: a project of the Kyushu University Liver Disease Study Group. *World J Gastroenterol* 2006; **12**: 784–90.
23 Furusyo N, Kajiwara E, Takahashi K *et al.* Association between the treatment length and cumulative dose of pegylated interferon alpha-2b plus ribavirin and their effectiveness as a combination treatment for Japanese chronic hepatitis C patients: Project of the Kyushu University Liver Disease Study Group. *J Gastroenterol Hepatol* 2008; **23**: 1094–104.
24 Sandres-Sauné K, Abravanel F, Nicot F *et al.* Detection and quantitation of HCV RNA using real-time PCR after automated sample processing. *J Med Virol* 2007; **79**: 1821–6.
25 Sizmann D, Boeck C, Boelter J *et al.* Fully automated quantification of hepatitis C virus (HCV) RNA in human plasma and human serum by the COBAS AmpliPrep/COBAS TaqMan system. *J Clin Virol* 2007; **38**: 326–33.
26 Furusyo N, Murata M, Ogawa E *et al.* Ribavirin concentration in the later stages of 48 week pegylated interferon-α2b plus ribavirin therapy for chronic hepatitis C is useful for predicting virological response. *J Antimicrob Chemother* 2011; **66**: 1127–39.
27 Hiramatsu N, Oze T, Yakushijin T *et al.* Ribavirin dose reduction raises relapse rate dose-dependently in genotype 1 patients with hepatitis C responding to pegylated interferon alpha-2b plus ribavirin. *J Viral Hepat* 2009; **16**: 586–94.
28 Kainuma M, Furusyo N, Kajiwara E *et al.* Pegylated interferon α-2b plus ribavirin for older patients with chronic hepatitis C. *World J Gastroenterol* 2010; **16**: 4400–9.
29 Okanoue T, Itoh Y, Minami M *et al.* Guidelines for the antiviral therapy of hepatitis C virus carriers with normal serum aminotransferase based on platelet counts. *Hepatol Res* 2008; **38**: 27–36.
30 Hsu CS, Liu CH, Liu CJ *et al.* Association of metabolic profiles with hepatic fibrosis in chronic hepatitis C patients with genotype 1 or 2 infection. *J Gastroenterol Hepatol* 2010; **25**: 970–7.
31 Ramcharran D, Wahed AS, Conjeevaram HS *et al.* Serum lipids and their associations with viral levels and liver disease severity in a treatment-naïve chronic hepatitis C type 1-infected cohort. *J Viral Hepat* 2011; **18**: 144–52.
32 Sangiovanni A, Morales R, Spinzi G *et al.* Interferon alfa treatment of HCV RNA carriers with persistently normal transaminase levels: a pilot randomized controlled study. *Hepatology* 1998; **27**: 853–6.
33 Puoti C, Castellacci R, Montagnese F. Hepatitis C virus carriers with persistently normal aminotransferase levels: healthy people or true patients? *Dig Liver Dis* 2000; **32**: 634–43.
34 Ohmiya M, Hayashi J, Ueno K *et al.* Effectiveness of interferon treatment for patients with chronic hepatitis C virus infection and normal aminotransferase levels. *Dig Dis Sci* 2000; **45**: 1953–8.
35 Lawson A. Hepatitis C virus-infected patients with a persistently normal alanine aminotransferase: do they exist and is this really a group with mild disease? *J Viral Hepat* 2010; **17**: 51–8.

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Original Article

Occurrence of clinical depression during combination therapy with pegylated interferon alpha or natural human interferon beta plus ribavirin

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Aim: The onset of depression symptoms during pegylated interferon α plus ribavirin (PEG-IFN/RBV) combination therapy has led to treatment discontinuation in some cases. In the present study, we conducted a questionnaire survey during treatment to determine whether natural human interferon β plus ribavirin (IFNβ/RBV) therapy is associated with a lower incidence of depression symptom onset compared with PEG-IFN/RBV therapy.

Methods: Seventy-seven patients with chronic hepatitis C received PEG-IFN/RBV (PR) or IFNβ/RBV (FR) therapy. A questionnaire survey was administered at the start of treatment, and at 4 and 12 weeks, using the Beck Depression Inventory II (BDI-II) and the Pittsburgh Sleep Quality Index (PSQI).

Results: BDI-II scores in the PR group increased at 4 and 12 weeks, but remained unchanged in the FR group. At 12 weeks, the mean BDI-II score and incidence of abnormalities with a BDI-II score of ≥14 were significantly lower in the FR group than in the PR group. BDI-II scores during IFNβ/RBV therapy in 11 patients currently using antidepressants remained unchanged up to 12 weeks. None of these 11 patients required addition or dose increases of antidepressants, and there was no evidence of worsened depression symptoms. Nine PR patients had BDI-II scores of ≥14 and PSQI scores of ≥11 at 12 weeks.

Conclusions: IFNβ/RBV therapy was associated with a lower incidence of depression symptom onset during treatment. In patients already diagnosed with depression, there was no evidence that IFNβ/RBV therapy caused any worsening of symptoms, indicating that IFNβ/RBV therapy is safe for patients with depression.

Key words: Beck Depression Inventory II, chronic hepatitis C, depression, natural interferon β, pegylated interferon α, Pittsburgh Sleep Quality Index.

INTRODUCTION

INTRODUCTION OF PEGYLATED interferon α plus ribavirin (PEG-IFN/RBV) combination therapy has led to an improved sustained virological response (SVR) in patients with chronic hepatitis C who are receiving interferon therapy.[1–6] An additional new treatment regimen has been introduced by adding Telaprevir to this PEG-IFN/RBV therapy.[7,8] However, adverse effects of PEG-IFN/RBV include the onset of symptoms of depression.[9–11] Thus, there are some difficulties in treating patients with depression or sleep disorders with PEG-IFN/RBV therapy.

In Japan, natural human interferon β (IFNβ), which has a low association with the onset of symptoms of depression, has been used in interferon therapy for chronic hepatitis C.[12,13] IFNβ plus ribavirin (IFNβ/RBV) combination therapy is now used.[14] However, there are no existing reports on the relationship between PEG-IFN/RBV or IFNβ/RBV therapy and the onset of depression symptoms. Therefore, in the present study, in order to determine if IFNβ/RBV therapy is associated with a lower incidence of the onset of symptoms of depression compared to PEG-IFN/RBV therapy, and to evaluate the safety of the IFNβ/RBV therapy in patients with depression, we conducted a questionnaire survey during PEG-IFN/RBV or IFNβ/RBV therapy to investigate the frequency, timing, and intensity of depression symptoms.

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METHODS

Study population

A TOTAL OF 77 Shinkokura Hospital patients with chronic hepatitis C who received IFN therapy for at least 12 weeks between January 2010 and April 2011 were included in the study. The study protocol was in compliance with both the Good Clinical Practice Guidelines and the 1975 Declaration of Helsinki, and was approved by the Institutional Review Board. Each patient gave informed consent before participating in this trial. Patients were assigned to one of the following three groups: (1) the PEG-IFN/RBV (PR) group, consisting of 41 patients who received PR therapy for a period of 24 to 48 weeks; (2) the IFNβ/RBV (FR) group, consisting of 25 patients who received the FR therapy for a period of 24 to 48 weeks; and (3) the FR-d group, consisting of 11 patients with depression who were on antidepressants and who received the FR therapy for a period of 24 to 48 weeks. Patients in the FR-d group received regular psychiatric consultation and experienced dose reduction, dose increase, or addition of antidepressants during treatment. Patients with depression, those with a previous history of depression, those who were on antidepressants, or those who were on sleep-inducing drugs were excluded from the PR and FR groups. Patients reporting some type of sleep disorder during treatment were given sleep-inducing drugs at the discretion of their primary physician. Treatment regimens of PR or FR therapy were determined by the physician. None of the patients required dose reduction of IFN due to neutropenia or thrombocytopenia prior to 12 weeks. This study is a prospective, non-randomized open trial.

Criteria for exclusion from the study were as follows: (i) clinical or biochemical evidence of hepatic decomposition and advanced cirrhosis identified by ascites, encephalopathy, or hepatocellular carcinoma; (ii) IFNβ/RBV: white blood cell count of less than 3000/mm^3 and platelet count of less than 50 000/mm^3, PEG-IFN/RBV: white blood cell count of less than 4000/mm^3 and platelet count of less than 80 000/mm^3; (iii) concomitant liver disease other than hepatitis C (hepatitis B surface antigen- or human immunodeficiency virus-positive); (iv) excessive active alcohol consumption exceeding 60 g/day or drug abuse; (v) severe psychiatric disease; and (vi) antiviral or corticosteroid therapy within the 12 months prior to enrollment.

Interferon treatment

Patients in the PR group received the following treatment regimen. In brief, PEG-IFNα-2b (PEG-Intron; MSD Co., Tokyo, Japan) was injected subcutaneously at a median dose of 1.5 lg/kg (range: 1.3–2.0 lg/kg) once a week. Ribavirin (Rebetol; MSD Co., Tokyo, Japan) was administered at a dose of 200–600 mg twice a day after breakfast and dinner (daily dose: 600–1000 mg). Patients in the FR and FR-d groups received the following treatment regimen. Briefly, IFNβ (Feron; Toray Industries Inc., Tokyo, Japan) was given intravenously at a dose of 6 million units (MU) daily for 4 weeks, followed by three times a week for 20–44 weeks. Ribavirin (Rebetol; MSD Co., Tokyo, Japan) was administered at a dose of 200–600 mg twice a day after breakfast and dinner (daily dose: 600–1000 mg). Hepatitis C virus (HCV) RNA concentrations were determined using the COBAS TaqMan HCV test (Roche Diagnostics). The linear dynamic range of the assay was 1.2–7.8 log IU/mL. Patients were considered to have an SVR if HCV RNA remained undetectable at 24 weeks after the completion of treatment. Urinalysis and measurement of serum albumin levels were performed once every 4 weeks, from the start of treatment to Week 24.

Questionnaire

A questionnaire survey was conducted immediately before the start of treatment and at 4 weeks and 12 weeks using the Beck Depression Inventory II (BDI-II) and the Pittsburgh Sleep Quality Index (PSQI).[15,16] The questionnaire survey was administered by one expert investigator, who remained blinded to the treatment regimens prescribed to patients, the timing of treatment, and other information. Patients with a BDI-II score of 14 or more were considered to have the onset of depression symptoms. Patients with a PSQI score of 11 or more were identified as having sleep disorder. All patients were given a questionnaire at 12 weeks, while a questionnaire was administered to 58 subjects at the baseline and at 4 weeks, including 28, 19, and 11 patients in the PR, FR, and FR-d groups, respectively.

Statistical analysis

Nonparametric tests (χ^2 test and Fisher's exact probability test) were used to compare the characteristics of the groups, as well as the BDI-II score and the PSQI score at 12 weeks. Univariate and multivariate logistic regression analyses were used to determine the factors that significantly contributed to the onset of symptoms of depression. The odds ratios (OR) and 95% confidence intervals (95% CI) were also calculated. All *P*-values less than 0.05, as determined by the two-tailed test, were considered significant. Variables were entered into

multiple logistic regression analysis to identify significant independent predictive factors. The potential pretreatment factors associated with patients having the onset of depression included the following variables: age, sex, HCV genotype, type of IFN, hemoglobin, platelet count, alanine aminotransferase (ALT), albumin, gamma-glutamyl transpeptidase (γ-GTP), total cholesterol, fasting blood sugar, and HCV RNA level.

RESULTS

Baseline background and IFN treatment

TABLE 1 SHOWS THE background of patients in the PR and FR groups. The mean age was significantly higher in the FR group (64.1 years) than in the PR group (52.5 years; $P < 0.001$). The PR group had more men than the FR group, although statistical significance was not reached. Baseline laboratory data showed a significantly lower platelet count in the FR group ($P < 0.05$). Significantly lower γ-GTP values were observed in the FR group ($P < 0.05$). The other laboratory parameters were comparable between the two groups. More patients with genotype 1 were in the PR group than the FR group, although no statistical significance was found. A total of 59 of 66 patients were evaluable for SVR. The proportion of patients with genotype 1 achieving an SVR was 33% (3/9) in the FR group and 48% (12/25) in the PR group. The PR group had a higher SVR rate, although statistical significance was not reached. The SVR rate among patients with genotype 2 was similar in the FR (85%, 11/13) and PR (83%, 10/12) groups. Over 24 weeks of treatment, 8% of patients (3/36) experienced at least one proteinuria event. None of the patients had a serum albumin level of ≤3.3 g/dL.

Change in the BDI-II score and the PSQI score during IFN treatment

Changes in the BDI-II score over time are shown in Figure 1. BDI-II scores in the PR group were increased relative to baseline at 4 and 12 weeks. Corresponding scores in the FR group remained unchanged. At 12 weeks, BDI-II scores were significantly lower in the FR group (5.8) than in the PR group (12.6; $P < 0.05$). The FR-d group had already high BDI-II scores of 23.0 at baseline, but BDI-II scores remained unchanged during treatment. No patients required dose increase or addition of antidepressants during treatment. There was no evidence of worsened depression symptoms during FR therapy.

In the PR group, the incidence of the onset of symptoms of depression, defined as a BDI-II score of 14 or more, increased from 0% at baseline to 21% at 4 weeks

Table 1 Clinical background before combination therapy of interferon β plus ribavirin (IFNβ/RBV) or pegylated interferon α plus ribavirin (PEG-IFN/RBV) in chronic hepatitis C patients

		IFNβ /RBV $n = 25$		PEG-IFN/RBV $n = 41$		IFNβ /RBV with depression $n = 11$	
Study variables		Mean	(SD)	Mean	(SD)	Mean	(SD)
Age	years	64.1	(12.7)**	52.5	(10.2)**	49.2	(9.7)
Gender							
Male		13	(52%)	30	(73%)	5	(45%)
Female		12	(48%)	11	(27%)	6	(55%)
Baseline hemoglobin	g/dL	14.0	(1.4)	14.7	(1.4)	14.0	(2.0)
Baseline platelet	10^9/L	165	(57)*	192	(59)*	202	(78)
Baseline ALT	IU/L	81.2	(81.1)	73.4	(64.0)	65	(43.1)
Baseline γ-GTP	IU/L	47.9	(36.5)*	92.0	(58.5)*	92.1	(96.3)
Baseline total cholesterol	mg/dL	177.1	(23.3)	177.5	(43)	201.5	(38.3)
Baseline fasting blood sugar	mg/dL	118.7	(58.4)	117.5	(33)	10.5.0	(30.8)
Baseline HCV	log IU/mL	5.8	(1.1)	6.1	(0.9)	5.9	(1.1)
HCV genotype							
1		12	(48%)	28	(68%)	5	(45%)
2		13	(52%)	13	(32%)	6	(55%)

*$P < 0.05$ (IFNβ/RBV vs. PEG-IFN/RBV).
**$P < 0.001$ (IFNβ/RBV vs. PEG-IFN/RBV).
ALT, alanine aminotransferase; HCV, hepatitis C virus; γ-GTP, albumin, gamma-glutamyl transpeptidase.

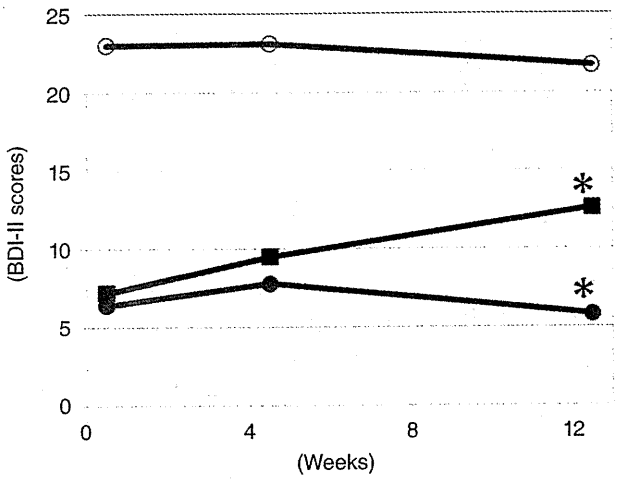

Figure 1 Changes in Beck Depression Inventory II (BDI-II) score for pegylated interferon α plus ribavirin (PEG-IFN/RBV) or interferon β plus ribavirin (IFNβ/RBV) therapy (●: IFNβ/RBV [FR] group, ○: FR-d group [FR patients with depression], ■: PEG-IFN/RBV [PR] group. *$P < 0.05$, FR vs. PR at week 12).

($n = 6$) and 34% at 12 weeks ($n = 14$). In the FR group, the incidence of the onset of symptoms of depression was 10% at 4 weeks ($n = 2$) and 8% at 12 weeks ($n = 2$), compared with 0% at baseline, indicating that the incidence did not change between 4 and 12 weeks. The incidence of the onset of depressive symptoms at 4 weeks was lower, but not significantly, in the FR group than in the PR group. Figure 2 shows the BDI-II score with a treatment regimen of IFN therapy at 12 weeks. The incidence of the onset of depressive symptoms (BDI-II score of 14 or more) was significantly lower in

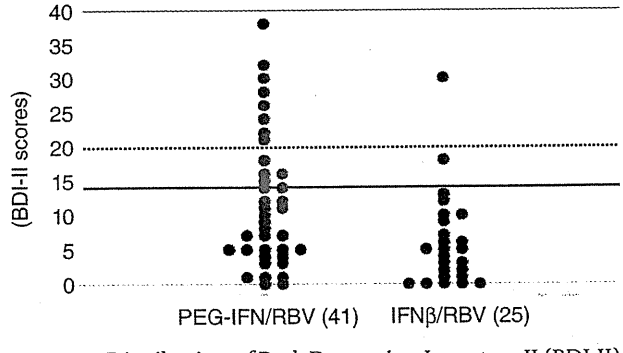

Figure 2 Distribution of Beck Depression Inventory II (BDI-II) scores for treatment regimens of interferon (IFN) therapy at 12 weeks (solid line: BDI-II score of 14, dotted line: BDI-II score of 20).

the FR group (8%, $n = 2$) than in the PR group (34%, $n = 14$; $P < 0.05$). The incidence of the onset of moderate depression symptoms (a BDI-II score of 20 or more) was higher in the PR group (20%, $n = 8$) than in the FR group (4%, $n = 1$). Mean PSQI scores at baseline, 4 weeks, and 12 weeks were 5.44, 6.62, and 7.37 in the PR group and 5.69, 6.01, and 6.88 in the FR group, respectively, indicating higher scores in the PR group than in the FR group from Week 4 onward. The incidence of sleep disorder, defined as a PSQI score of 11 or more, was higher in the PR group at both 4 and 12 weeks (18% and 27%, respectively) than in the FR group (0% and 8%, respectively).

BDI-II score and PSQI score at 12 weeks

Figure 3 shows the correlation between the BDI-II score and the PSQI score at 12 weeks. Some correlation was found between these scores with an overall coefficient of correlation (r) of 0.6755 ($P < 0.0001$). A strong correlation was noted between the BDI-II score and the PSQI score in the PR group, with an r-value of 0.7586 ($P < 0.0001$). In contrast, no correlation was observed in the FR group, with an r-value of 0.3589 ($P = 0.0786$). The incidence of sleep disorder (a PSQI score of 11 or more) at 12 weeks was lower in the FR group (8%, $n = 2$) than in the PR group (27%, $n = 11$). Only nine patients in the PR group had a BDI-II score of 14 or more and a PSQI score of 11 or more, whereas there were no such patients in the FR group, with the difference reaching statistical significance ($P < 0.05$). Three of the nine patients with a BDI-II score of 14 or more

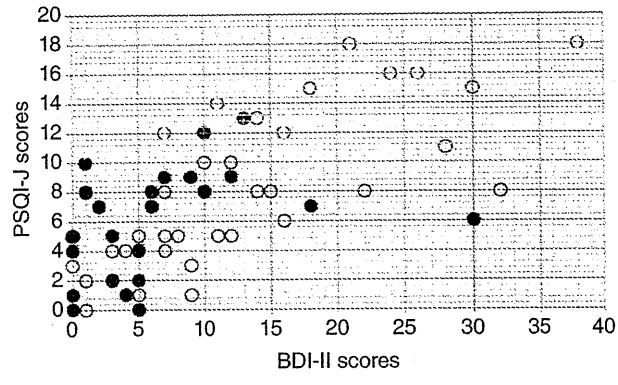

Figure 3 Graph showing correlation between Beck Depression Inventory II (BDI-II) and the Pittsburgh Sleep Quality Index (PSQI) scores at 12 weeks (correlation coefficient, Total: r = 0.6755, $P < 0.0001$; pegylated interferon α plus ribavirin [PEG-IFN/RBV]: r = 0.7586, $P < 0.0001$; interferon β plus ribavirin [IFNβ/RBV]: r = 0.3589, $P = 0.0786$).

and a PSQI score of 11 or more at 12 weeks discontinued treatment prior to 24 weeks due to depression symptoms.

Predictive factors contributing to the onset of depression symptoms during IFN therapy

Results from univariate and multivariate logistic regression analyses of the factors contributing to the onset of depression symptoms during IFN therapy are shown in Table 2. The univariate regression analysis showed that the type of IFN (PEG-IFNα) was the only factor that contributed to the onset of depressive symptoms ($P < 0.027$). The multivariate logistic regression analysis confirmed that the type of IFN (PEG-IFNα/RBV) was the only contributing significant independent predictive factor.

DISCUSSION

PR THERAPY FOR chronic hepatitis C involves long-term treatment, ranging from 24 to 48 weeks. The duration of treatment in patients with HCV genotype 1 and a high viral load may range from 48 and 72 weeks.[17] Currently available PR therapy yields only a low SVR rate in patients who discontinue treatment early. Thus, it is important to complete treatment as prescribed. The onset of depression symptoms associated with PEG-IFNα treatment is one of the reasons for early discontinuation of treatment due to adverse effects. In Japan, IFNβ, which is associated with a low incidence of the onset of depression symptoms, has been used in patients with depression.[12–14] In addition, due to the milder side effects of IFNβ, we have used it in IFN therapy for hemodialyzed patients with chronic hepatitis C.[18] The SVR rate among patients with HCV genotype 1 who were treated with IFNβ/RBV was lower (approximately 40%) than that among those treated with PEG-IFN/RBV[11], while patients with HCV genotype 2 who were treated with IFNβ/RBV had an SVR rate of approximately 87%, which was similar to that observed in those treated with PEG-IFN/RBV [19].

There have been no reported studies on the relationship between FR therapy and the onset of depression symptoms. In the present study, we demonstrated that FR therapy produced a significantly lower frequency of depression symptoms than PR therapy. We also found no evidence of worsened depression symptoms during the FR therapy in patients with depression.

In the present study, a questionnaire was conducted using BDI-II and PSQI scores to assess depression symptoms and sleep disorder. The BDI-II is way to measure the severity of depression symptoms and consists of 21 questions. Symptoms with a total score of ≥14, ≥20, and ≥29 are considered mild, moderate, and severe, respectively.[15] The PSQI is a questionnaire that is used to measure the quality of sleep. Original versions of both questionnaires have been translated into Japanese, and the translated versions were used in our study.

In the present study, we found that the percentage of patients with a BDI-II score of 14 or more in the PR group was approximately 20% as early as 4 weeks after

Table 2 Results from univariate and multivariate logistic regression analyses of the factors contributing to the onset of depressive symptoms

			Simple regression		Multiple logistic regression	
Factor	Range		Odds ratio	*P*-value	Odds ratio	*P*-value
Age	≧60 / <60	(years)	0.308	0.066	–	–
Sex	Male / Female		0.808	0.728	–	–
Genotype	1 / 2		0.900	0.859	–	–
Type of IFN	PEG-IFN/IFNβ		0.168	0.027	0.168	0.027
Hemoglobin	<14 / ≧14	(g/dL)	1.310	0.647	–	–
Platelet	<15 / ≧15	(10^4/μL)	3.294	0.143	–	–
ALT	≧50 / <50	(IU/L)	1.269	0.682	–	–
γ-GTP	≧45 / <45	(IU/L)	0.990	0.986	–	–
Total cholesterol	≧220 / <220	(mg/dL)	1.667	0.652	–	–
FBS	<110 / ≧110	(mg/dL)	0.682	0.531	–	–
Viral load	≧6.0 / <6.0	(LogIU/mL)	0.829	0.750	–	–

ALT, alanine aminotransferase; FBs, fasting blood sugar; IFN, interferon; γ-GTP, gamma-glutamyl transpeptidase; PEG-IFN/RBV, pegylated interferon α plus ribavirin.

the start of treatment and increased to 34% within the first 12 weeks. However, in the FR group, 10% or less of patients only experienced the onset of mild depressive symptoms and the percentage was comparable at 4 and 12 weeks, after which no patients discontinued treatment due to depression symptoms. At 12 weeks particularly, both the mean BDI-II score and the incidence of abnormalities (a BDI-II score of 14 or more) were significantly lower in the FR group than in the PR group, indicating that FR therapy was less likely to induce the onset of depression symptoms than PR therapy. It appears that assessing the onset of depressive symptoms is useful at 12 weeks of IFN treatment. However, assessment at 4 weeks of treatment also appears to be necessary, when possible, because the onset of depression symptoms may be observed as early as 4 weeks.

The onset of depression symptoms during PR therapy has been associated with sleep disorder. In the present study, there was a strong association between the BDI-II scores and PSQI scores. Careful management is required in patients reporting sleep disorder, which is one of the early symptoms of depression.

Some of the patients receiving PR therapy, who had a BDI-II score of 14 or more and a PSQI score of 11 or more at 12 weeks, discontinued treatment due to the subsequent onset of depressive symptoms; more careful management is required in these patients.

Patients with depression were also included in the present study (FR-d group). There was no increase over time in the BDI-II score of patients with depression and none of the patients with depression required additional or an increased dose of antidepressants; there was no evidence that the depression symptoms worsened. This suggests that FR therapy is safe in both patients with depression and patients at risk for symptoms of depression.

The BDI-II and the PSQI, which were used in the present study, are simple questionnaires, which take several minutes to complete and appear to be useful instruments in assessing the onset of depressive symptoms during IFN therapy. IFNβ/RBV therapy should be used in patients with depression or sleep disorder. Patients showing the onset of depression or sleep disorder during PEG-IFN/RBV therapy should be switched to IFNβ/RBV therapy to continue IFN therapy, having given due consideration to the discontinuation of therapy.

IFNB/RBV THERAPY WAS associated with a low incidence of the onset of depression symptoms during treatment, and was also safe in patients with depression, who showed no evidence of worsening of symptoms during treatment. Depression symptoms during PEG-IFN/RBV therapy were strongly associated with sleep disorders and commonly occurred within the first 12 weeks of treatment. Patients with the onset of both symptoms of depression and sleep disorders should be closely monitored, as they are more likely to discontinue treatment after these conditions develop.

REFERENCES

1 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358:** 958–65.

2 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347:** 975–82.

3 Nomura H, Miyagi Y, Tanimoto H, Higashi M, Ishibashi H. Effective prediction of outcome of combination therapy with pegylated interferon alpha 2b plus ribavirin in Japanese patients with genotype-1 chronic hepatitis C using early viral kinetics and new indices. *J Gastroenterol* 2009; **44:** 338–45.

4 Nomura H, Miyagi Y, Tanimoto H, Ishibashi H. Impact of early viral kinetics on pegylated interferon alpha 2b plus ribavirin therapy in Japanese patients with genotype 2 chronic hepatitis C. *J Viral Hepat* 2009; **16:** 346–51.

5 Kumada H, Okanoue T, Onji M *et al.* The Study for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis, Ministry of Health, Labor and Welfare of Japan: guideline for the treatment of chronic hepatitis and cirrhosis due to hepatitis C virus infection for the fiscal year 2008 in Japan. *Hepatol Res* 2010; **40:** 8–13.

6 Kainuma M, Furusyo N, Kajiwara E *et al.* Kyushu University Liver Disease Study Group. Pegylated interferon α-2b plus ribavirin for older patients with chronic hepatitis C. *World J Gastroenterol* 2010; **16:** 4400–9.

7 Akuta N, Suzuki F, Hirakawa M *et al.* Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin. *Hepatology* 2010; **52:** 421–9.

8 Chayama K, Hayes CN, Abe H *et al.* IL28B but not ITPA polymorphism is predictive of response to pegylated interferon, ribavirin, and telaprevir triple therapy in patients with genotype 1 hepatitis C. *J Infect Dis* 2011; **204:** 84–93.

9 Scalori A, Pozzi M, Bellia V *et al.* Interferon-induced depression: prevalence and management. *Dig Liver Dis* 2005; **37:** 102–7.

10 Schaefer M, Schwaiger M, Garkisch AS *et al.* Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. *J Hepatol* 2005; **42:** 793–8.

11 Zdilar D, Franco-Bronson K, Buchler N, Locala JA, Younossi ZM. Hepatitis C, interferon alfa, and depression. *Hepatology* 2000; **31:** 1207–11.

12 Asahina Y, Izumi N, Uchihara M *et al.* A potent antiviral effect on hepatitis C viral dynamics in serum and peripheral blood mononuclear cells during combination therapy with high-dose daily interferon alfa plus ribavirin and intravenous twice-daily treatment with interferon beta. *Hepatology* 2001; **34**: 377–84.
13 Nomura H, Sou S, Nagahama T, Hayashi J, Kashiwagi S, Ishibashi H. Efficacy of early retreatment with interferon beta for relapse in patients with genotype Ib chronic hepatitis C. *Hepatol Res* 2004; **28**: 36–40.
14 Arase Y, Suzuki F, Akuta N *et al.* Efficacy and safety of combination therapy of natural human interferon beta and ribavirin in chronic hepatitis C patients with genotype 1b and high virus load. *Intern Med* 2010; **49**: 957–63.
15 Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess* 1996; **67**: 588–97.
16 Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatr Res* 1998; **28**: 193–213.
17 Berg T, von Wagner M, Nasser S *et al.* Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006; **130**: 1086–97.
18 Zeniya M, Yokoyama K, Imamura N *et al.* Significance of interferon-beta for the treatment of hepatitis C virus infection in hemodialyzed patients. *Hepatol Res* 2010; **40** (9): 862–9.
19 Arase Y, Suzuki F, Akuta N *et al.* Efficacy and safety of combination therapy of natural human interferon beta and ribavirin in chronic hepatitis C patients with genotype 2 and high virus load. *Intern Med* 2010; **49**: 965–70.

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Original Article

Recommendation of lamivudine-to-entecavir switching treatment in chronic hepatitis B responders: Randomized controlled trial

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Aim: In the 2007–2008 guidelines of the study group (Ministry of Health, Labor and Welfare of Japan), lamivudine (LAM)-continuous treatment was recommended in patients treated with LAM for more than 3 years who maintained hepatitis B virus (HBV) DNA less than 2.6 log copies/mL, because in these patients LAM resistance might exist and switching treatment to entecavir (ETV) might cause ETV resistance. However, there was no evidence on whether switching treatment to ETV- or LAM-continuous treatment was better in those patients. In the present study, we performed a randomized controlled trial of LAM-to-ETV switching treatment.

Methods: Twenty-seven patients treated with LAM for more than 3 years whose HBV DNA levels were less than 2.6 log copies/mL were enrolled and randomly divided into two groups, LAM-continued group or switching to ETV group. Then, we examined incidence of virological breakthrough (VBT) and breakthrough hepatitis (BTH) in each group.

Results: There was no BTH in any of the patients. VBT was observed in six patients of the LAM group (6/15, 40%), and no patient of the ETV group (0/11, 0%) ($P = 0.02$). The differences of the proportion of cumulated VBT using a log–rank test with Kaplan–Meier analysis were significant between the LAM and ETV groups ($P = 0.025$).

Conclusion: In patients treated with LAM for more than 3 years maintaining HBV DNA less than 2.6 log copies/mL, switching treatment to ETV is recommended at least during the 2 years' follow-up period.

Key words: chronic hepatitis B, entecavir, lamivudine, lamivudine resistance, randomized controlled trial, switching treatment

INTRODUCTION

OVER THE PAST two decades, treatment of chronic hepatitis B (CHB) has greatly improved with the availability of nucleos(t)ide analogs (NA), including lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine, clevudine and tenofovir. NA target

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the reverse transcriptase of hepatitis B virus (HBV), and are highly effective in suppressing HBV replication and clinical progression to liver cirrhosis and hepatocellular carcinoma in CHB patients.[1–4]

Lamivudine, ADV and ETV are commonly available in Japan. LAM, the first approved NA, has been shown to provide benefit for CHB patients with respect to the reduction of HBV DNA, normalization of alanine aminotransferase (ALT) and improvement of liver histology.[5,6] However, a serious problem of LAM is the high incidence of drug resistance during long-term treatment. The detection rate of LAM resistance has been reported to be 24% at 1 year and 70% after 5 years of treatment.[7–10] Even when the HBV DNA level was maintained at less than 2.6 log copies/mL, the accumulated incidence of LAM resistance reached 65% in patients treated with LAM for a long period (3 to ~10 years).[11] LAM resistance is caused by amino acid substitution(s) at rtM204V/I within the reverse transcriptase domain of the HBV polymerase gene.[12–14] The emergence of a LAM-resistant strain leads to virological breakthrough (VBT) and breakthrough hepatitis (BTH).

Recently, ETV has been demonstrated to exert antiviral efficacy in both NA-naïve and LAM-resistant CHB patients.[15–17] The frequency of ETV resistance has been reported to be 1.2% after 5 years of treatment in NA-naïve CHB patients.[18,19] On the other hand, in switching treatment to ETV for LAM-resistant CHB patients, the cumulative probability of ETV resistance increases.[17,20] After 5 years of treatment, 51% of LAM-refractory patients treated with ETV showed genotypic ETV resistance.[21]

The 2007–2008 guidelines of the study group (Ministry of Health, Labor and Welfare of Japan) for patients on LAM therapy are summarized in Table 1.[22] Regardless of duration of LAM administration, in cases where HBV DNA is more than 2.6 log copies/mL with BTH, ADV add-on treatment was recommended. In patients treated with LAM for less than 3 years who maintained HBV DNA of less than 2.6 log copies/mL or HBV DNA of 2.6 log copies/mL or more without BTH, switching to ETV was recommended. On the other hand, in patients treated with LAM for more than 3 years who maintained HBV DNA of less than 2.6 log copies/mL or HBV DNA of 2.6 log copies/mL or more without BTH, LAM-continuous treatment was recommended because in these patients LAM resistance might exist, and switching treatment to ETV might cause ETV resistance. However, there is insufficient evidence on whether switching treatment to ETV- or LAM-continuous treatment is better for CHB patients treated with LAM for more than 3 years with HBV DNA of less than 2.6 log copies/mL.

In the present study, we performed a randomized controlled trial of LAM-to-ETV switching treatment in CHB patients treated with LAM for more than 3 years who maintained HBV DNA of less than 2.6 log copies/mL.

METHODS

Patients

A TOTAL OF 27 CHB patients (mean age 55 ± 9 years, 17 men) from 11 institutions all over Japan (Hokkaido University Hospital, Tohoku University Hospital, Akita City Hospital, Kuramitsu Clinic, Juntendo University Hospital, Chukyo Hospital, Nagoya City University Hospital, Okayama University Hospital, Kawasaki Medical University Hospital, Ehime University Hospital, Shin-Kokura Hospital) were enrolled from April 2008. All the patients were followed at least 6 months after they were diagnosed with CHB. Their characteristics are shown in Table 2. They were treated with LAM (100 mg/day) for more than 3 years (median 50 months, range 36–106 months). Before starting LAM administration, all patients were positive for hepatitis B surface antigen (HBsAg) in serum, abnormal for ALT, detectable for HBV DNA, and were not

Table 1 2007–2008 guidelines of the study group (Ministry of Health, Labor and Welfare of Japan) for patients on lamivudine treatment

Duration of lamivudine treatment HBV DNA		<3 years	≥3 years
<2.6 log copies/mL, persistently		May be switched to ETV 0.5 mg/day	LAM 100 mg/day
≥2.6 log copies/mL	No BTH†	May be switched to ETV 0.5 mg/day	LAM 100 mg/day
	With BTH	Add on ADV 10 mg/day	Add on ADV 10 mg/day

†After checking for absence of LAM resistance.
ADV, adefovir; BTH, breakthrough hepatitis; ETV, entecavir; HBV, hepatitis B virus; LAM, lamivudine.

Table 2 Characteristics of LAM continuous group and ETV switch group at baseline

	LAM ($n = 15$)	ETV ($n = 11$)	*P*-value
Male	10	6	NS
Age	53 ± 7	57 ± 7	NS
Duration of LAM administration (month)	59 ± 23	55 ± 18	NS
ALT (IU/L)	33 ± 29	28 ± 22	NS
HbeAg positive	1	1	NS

ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e-antigen; LAM, lamivudine; NS, not significant.

infected with hepatitis C virus and HIV. Patients diagnosed with alcoholism, primary biliary cirrhosis or autoimmune hepatitis were excluded.

Study design

The overview of this study design is shown in Figure 1. Twenty-seven patients treated with LAM for more than 3 years were enrolled, who showed HBV DNA of less than 2.6 log copies/mL at entry. They were randomly divided into two groups by each institution, the LAM-continued group (LAM group) or switching to the ETV group (ETV group). The primary end-points were the incidences of VBT and BTH in each group. VBT was defined as having more than 1 log copies/mL increase of HBV DNA level from the nadir on at least two occasions after initial virological response. BTH was defined as showing abnormal ALT level due to LAM or ETV resistance. All subjects were monitored at least every 3-month intervals. At every visit, routine examination with biochemical (ALT, bilirubin, albumin) and virological (HBV DNA level, hepatitis B e-antigen [HBeAg], anti-HBe) assessments took place. The mean follow-up period was 24 ± 3 months.

This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) on 4 April 2008 as "A randomized trial of lamivudine continuous therapy and entecavir switching therapy for chronic hepatitis B patients treated with lamivudine monotherapy" (no. UMIN000001120).

The study protocol conformed to the Declaration of Helsinki, and was approved by the Committee for Ethics of Medical Experiments on Human Subjects of all the institutions, and written informed consent was obtained from every participant.

Serological and virological markers of HBV

Hepatitis B surface antigen, antibody against HBsAg (anti-HBs), HBeAg and antibody against HBeAg (anti-HBe) were determined using commercially available enzyme immunoassays. HBV DNA was determined by an Amplicor HBV Monitor (Roche Molecular Systems, Branchburg, NJ, USA; detection limit 2.6 log copies/mL)

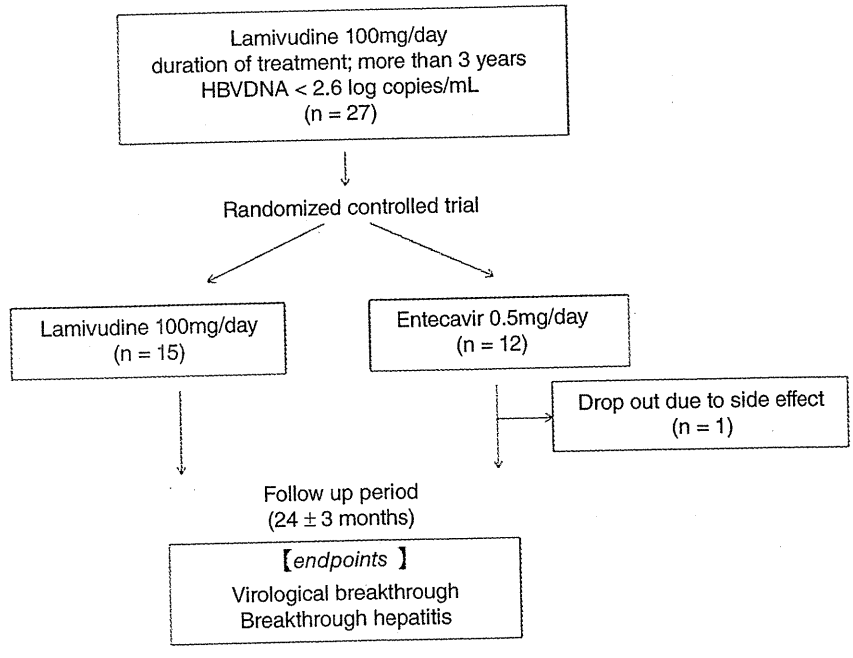

Figure 1 Overview of this study design. Twenty-seven patients treated with lamivudine for more than 3 years whose hepatitis B virus (HBV) DNA was maintained at <2.6 log copies/mL were enrolled. They were randomly divided into two groups by each institution, lamivudine-continued group or switching to entecavir group. We examined the incidence of virological breakthrough and breakthrough hepatitis in each group.

or COBAS AmpliPrep-COBAS TaqMan HBV test (Roche Molecular Systems; detection limit 2.1 log copies/mL). Positive results (signals) below the quantitative HBV DNA concentrations are referred to as "detected" and negative signals are "not detected" when registered by COBAS AmpliPrep-COBAS TaqMan HBV test. The presence of LAM-resistant rtM204V/I and rtL180M substitutions was analyzed by direct sequencing of the HBV DNA polymerase reverse transcriptase site.

Retrospective analysis

Using a conserved serum sample, we examined the existence of LAM-resistant rtM204V/I or rtL180M at baseline in patients with VBT. We also measured HBV DNA by COBAS AmpliPrep-COBAS TaqMan HBV test, and we evaluated the subsequent occurrence of VBT according to the DNA level (not detected/detected/2.1 to <2.6 log copies/mL).

Statistical analysis

Categorial variables were compared between groups by the χ^2-test or Fisher's exact test, and non-categorical variables by Mann–Whitney's *U*-test. The cumulated VBT rate was compared between each group using a log–rank test with Kaplan–Meier analysis. All data were analyzed using SPSS ver. 15.0J software. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the patients

BASED ON THIS randomized controlled trial, 12 patients were placed in an ETV group and 15 in a LAM group. One patient in the ETV group dropped out because of skin rash by ETV. The baseline characteristics of the patients are described in Table 2. At the entry, one patient was positive for HBeAg in each group. There was no difference in sex, age, duration of LAM administration and ALT level between the two groups.

Incidence of VBT and BTH

There was no BTH in any of the patients. The incidence of VBT was six patients out of 15 (40%) in the LAM group, and no patient in the ETV group ($P = 0.02$). The Kaplan–Meier curve for the proportion of cumulated VBT is shown in Figure 2. The differences in the rates of VBT were significant between the LAM and ETV groups (log–rank test $P = 0.025$).

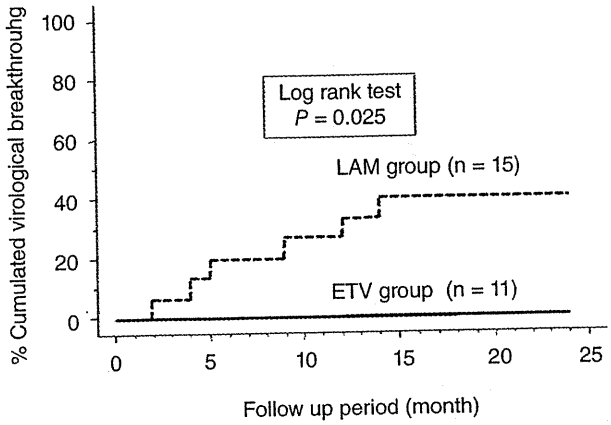

Figure 2 Proportion of cumulated virological breakthrough in lamivudine (LAM) and entecavir (ETV) group. The cumulated rate of virological breakthrough was higher in patients treated with LAM than those with ETV (40% vs 0%, $P = 0.025$ by log–rank test).

Characteristics of patients with VBT in LAM group

Details of the six VBT cases in the LAM group are described in Table 3. Assessment of LAM-resistant mutations at the time of VBT showed that both rtM204V and rtL180M were observed in all cases. For five of the six cases, HBV DNA was detected by COBAS AmpliPrep-COBAS TaqMan HBV test at baseline, although the HBV DNA level was very low. With respect to LAM-resistant mutation at baseline, rtM204V and rtL180M were observed in one of six cases. In contrast, no LAM-resistant mutations were observed in 20 non-VBT cases at baseline.

Incidence of VBT based on the HBV DNA level by COBAS AmpliPrep-COBAS TaqMan HBV test

Incidence of VBT based on the HBV DNA level according to COBAS AmpliPrep-COBAS TaqMan HBV test at baseline is shown in Figure 3. HBV DNA levels were less than 2.6 log copies/mL by Amplicor HBV Monitor in all cases. However, HBV DNA levels in the LAM group were "not detected" in five cases, "detected" in eight cases and 2.1 log copies/mL or more in two cases by COBAS AmpliPrep-COBAS TaqMan HBV test. VBT was observed in five of the 10 cases whose results were either "detected" or 2.1 log copies/mL or more and in one of the five "not detected" cases. On the other hand, although HBV DNA levels in the ETV group were

Table 3 Characteristics of patients with virological breakthrough in LAM group

			At baseline			At virological breakthrough		
Age	Sex	Duration of LAM administration (month)	HBeAg	HBV DNA by TaqMan HBV (log copies/mL)	Mutant of LAM resistance	Period of VBT (months)	HBV DNA (log copies/mL)	Mutant of LAM resistance
49	M	37	Negative	Detected	None	14	4.9	L180M/M204V
54	F	106	Negative	Detected	None	5	2.8	L180M/M204V
63	F	81	Negative	Not detected	None	9	4.5	L180M/M204V
57	F	43	Negative	Detected	None	10	3	L180M/M204V
55	M	84	Negative	Detected	None	12	2.8	L180M/M204V
57	M	36	Negative	2.3	L180M/M204V	2	4	L180M/M204V

ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; LAM, lamivudine; VBT, virological breakthrough.

"detected" in six cases by COBAS AmpliPrep-COBAS TaqMan HBV test, there was no incidence of VBT: HBV DNA levels of five patients were undetectable and that of one patient was "detected" at the last follow-up point after switching to ETV.

DISCUSSION

AT PRESENT, LAM, ADV and ETV are only approved for treatment of CHB patients in Japan. ETV has become the first-line treatment for NA-naïve patients, because the ETV resistance is much less frequent than LAM-resistance.[8,23,24] On the other hand, in switching treatment to ETV for LAM-resistant CHB patients, the frequency of ETV resistance was increased.[17,20,25–27] It has also been reported that ADV add-on treatment suppressed HBV replication more effectively than ETV or ADV monotherapy in patients with LAM-resistant CHB.[25,28] Therefore, it is desirable to examine LAM-resistant mutants before switching to ETV in patients treated with LAM. However, as the assay for the LAM-resistant mutants is not covered by the Japanese health insurance system at present, the Japanese guidelines for CHB management after LAM therapy were based on HBV DNA, duration of LAM administration and incidence of BTH (Table 1).[22] In patients treated with LAM for more than 3 years, maintaining HBV DNA of less than 2.6 log copies/mL or HBV DNA of 2.6 log copies/mL or more without BTH, LAM-continuous treatment was recommended because in these patients, LAM-resistance might exist, and switching treatment to ETV might cause ETV-resistance. It was reported that although LAM-resistant strains were detected in 34% cases treated with LAM for more than 3 years and whose HBV DNA level was suppressed to less than 2.6 log copies/mL, switching to ETV maintained undetectable HBV DNA level over 2 years.[29] In addition, Kurashige *et al.* reported that LAM-to-ETV switching treatment maintained an undetectable HBV DNA level in patients with baseline HBV DNA of less than 2.6 and 2.6 to less than 4.0 log copies/mL for a period of ETV treatment ranging 10–23 (median 20) months.[30] In the present study, randomized controlled trial evidenced that switching treatment to ETV or LAM-continuous treatment would be recommended in CHB patients treated with LAM for more than 3 years and maintained HBV DNA of less than 2.6 log copies/mL. Interestingly, even though HBV DNA had been suppressed to less than 2.6 log copies/mL, a high rate of VBT was observed in the LAM group, whereas no VBT over 24 months was observed in the ETV group. Of the six patients with VBT,

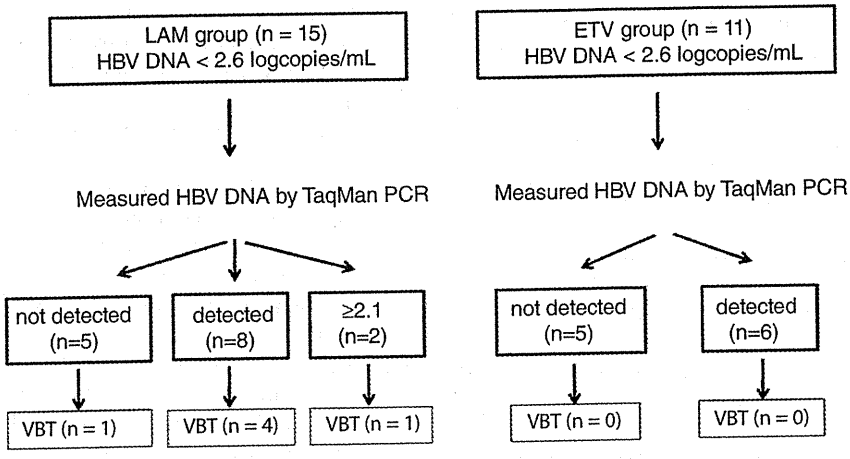

Figure 3 Incidence of virological breakthrough (VBT) based on the hepatitis B virus (HBV) DNA level at baseline by COBAS AmpliPrep-COBAS TaqMan HBV test (TaqMan PCR). The subsequent occurrence of VBT according to the DNA level by TaqMan PCR (not detected/detected/2.1 to <2.6 log copies/mL) was evaluated. In the lamivudine (LAM) group, VBT was observed in five of the 10 cases in which the results were either "detected" or ≥2.1 log copies/mL and in one of the five "not detected" cases. On the other hand, HBV DNA levels in the entecavir (ETV) group were "detected" in six, but there was no incidence of VBT.

five had no LAM resistance at baseline. However, the LAM resistance of rtM204V and rtL180M were found in all the patients with VBT in the LAM group. Moreover, a retrospective assessment by COBAS AmpliPrep-COBAS TaqMan HBV test showed that HBV DNA was detectable in 10 patients in the LAM group and six patients in the ETV group. Only five of the 10 patients in the LAM group had VBT, but none in the ETV group. In addition, one patient had VBT in the LAM group even though DNA was not detected by the TaqMan test, suggesting that switching to ETV was preferable. Hence, our data supported the 2010 Japanese guidelines which recommend switching to ETV in patients whose HBV DNA levels are less than 2.1 log copies/mL by TaqMan PCR.

A potential limitation of the present study is that the number of the cases was small. Nevertheless, our randomized controlled trial indicated significant difference in the incidence of VBT between the LAM and ETV groups. Therefore, this study is valuable for the purpose of verifying the 2007–2008 guidelines in Japan. In the present study, although no LAM-resistant mutant was observed in the ETV group at baseline, a very low level of LAM-resistant mutants may derive ETV resistance for long-term therapy. The results of switching to ETV in the present study were favorable during the 24-month observation period, but we have to be careful of possible emergence of ETV-resistant mutants in long-term follow up.

In conclusion, in patients treated with LAM for more than 3 years maintaining HBV DNA of less than 2.6 log copies/mL, switching treatment to ETV is recommended in at least a 2-year follow-up period.

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REFERENCES

1 Liaw YF, Sung JJ, Chow WC *et al.* Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; **351**: 1521–31.
2 Liaw YF. Hepatitis B virus replication and liver disease progression: the impact of antiviral therapy. *Antivir Ther* 2006; **11**: 669–79.
3 Di Marco V, Marzano A, Lampertico P *et al.* Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. *Hepatology* 2004; **40**: 883–91.
4 Papatheodoridis GV, Dimou E, Dimakopoulos K *et al.* Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine. *Hepatology* 2005; **42**: 121–9.

5 Lai CL, Chien RN, Leung NW *et al.* A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med* 1998; **339**: 61–8.
6 Dienstag JL, Schiff ER, Wright TL *et al.* Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999; **21** (341): 1256–63.
7 Lai CL, Dienstag J, Schiff E *et al.* Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. *Clin Infect Dis* 2003; **36**: 687–96.
8 Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661–2.
9 Lok AS, Lai CL, Leung N *et al.* Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003; **125**: 1714–22.
10 Chang TT, Lai CL, Chien RN *et al.* Four years of lamivudine treatment in Chinese patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2004; **19**: 1276–82.
11 Kobayashi M, Suzuki F, Akuta N *et al.* Correlation of YMDD mutation and breakthrough hepatitis with hepatitis B virus DNA and serum ALT during lamivudine treatment. *Hepatol Res* 2010; **40**: 125–34.
12 Allen MI, Deslauriers M, Andrews CW *et al.* Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. Lamivudine Clinical Investigation Group. *Hepatology* 1998; **27**: 1670–7.
13 Liaw YF, Chien RN, Yeh CT, Tsai SL, Chu CM. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology* 1999; **30**: 567–72.
14 Westland CE, Yang H, Delaney W *et al.* Activity of adefovir dipivoxil against all patterns of lamivudine-resistant hepatitis B viruses in patients. *J Viral Hepat* 2005; **12**: 67–73.
15 Chang TT, Gish RG, de Man R *et al.* A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006; **354**: 1001–10.
16 Lai CL, Shouval D, Lok AS *et al.* Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006; **354**: 1011–20.
17 Sherman M, Yurdaydin C, Sollano J *et al.* Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. *Gastroenterology* 2006; **130**: 2039–49.
18 Colonno RJ, Rose R, Baldick CJ *et al.* Entecavir resistance is rare in nucleoside naive patients with hepatitis B. *Hepatology* 2006; **44**: 1656–65.
19 Tenney DJ, Rose RE, Baldick CJ *et al.* Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. *Hepatology* 2009; **49**: 1503–14.
20 Sherman M, Yurdaydin C, Simsek H *et al.* Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. *Hepatology* 2008; **48**: 99–108.
21 Tenney DJ, Pokornowski K, Rose RE *et al.* Entecavir at five years shows long-term maintenance of high genetic barrier to hepatitis B virus resistance. *Hepatol Int* 2008; **2**: S302–3.
22 Kumada H, Okanoue T, Onji M *et al.* Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis B virus infection for the fiscal year 2008 in Japan. *Hepatol Res* 2010; **40**: 1–7.
23 Liaw YF, Leung N, Kao JH *et al.* Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008; **2**: 263–83.
24 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. *J Hepatol* 2009; **50**: 227–42.
25 Reijnders JG, Deterding K, Petersen J *et al.* Antiviral effect of entecavir in chronic hepatitis B: influence of prior exposure to nucleos(t)ide analogues. *J Hepatol* 2010; **52**: 493–500.
26 Suzuki Y, Suzuki F, Kawamura Y *et al.* Efficacy of entecavir treatment for lamivudine-resistant hepatitis B over 3 years: histological improvement or entecavir resistance? *J Gastroenterol Hepatol* 2009; **24**: 429–35.
27 Mukaide M, Tanaka Y, Shin IT *et al.* Mechanism of entecavir resistance of hepatitis B virus with viral breakthrough as determined by long-term clinical assessment and molecular docking simulation. *Antimicrob Agents Chemother* 2010; **54**: 882–9.
28 Kim HJ, Park JH, Park DI *et al.* Rescue therapy for lamivudine-resistant chronic hepatitis B: comparison between entecavir 1.0 mg monotherapy, adefovir monotherapy and adefovir add-on lamivudine combination therapy. *J Gastroenterol Hepatol* 2010; **25**: 1374–80.
29 Suzuki F, Akuta N, Suzuki Y *et al.* Efficacy of switching to entecavir monotherapy in Japanese lamivudine-pretreated patients. *J Gastroenterol Hepatol* 2010; **25**: 892–8.
30 Kurashige N, Ohkawa K, Hiramatsu N *et al.* Lamivudine-to-entecavir switching treatment in type B chronic hepatitis patients without evidence of lamivudine resistance. *J Gastroenterol* 2009; **44**: 864–70.

C型肝炎

C型肝炎の抗ウイルス療法の実際

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はじめに

1992年よりC型慢性肝炎に対してのインターフェロンinterferon(IFN)治療が開始された．当時は，IFN単独24週間治療であった．日本ではC型肝炎ウイルスhepatitis C virus(HCV)の型は1型と2型が多く，ウイルス量も測定可能である．このウイルスの型によりIFN治療効果が異なる．1型は2型に比べIFN治療に抵抗性である．このため1型・高ウイルス例は難治例と呼ばれている．IFN単独24週間治療では，難治症例の著効sustained virological response(SVR)率は約10%前後である．2004年12月よりペグインターフェロンとリバビリン併用療法peg-interferon plus ribavirin(PEG-IFN/RBV)が開始され，1型・高ウイルス例においてもSVR率は40%から50%と改善し，2型・高ウイルス例では80%以上のSVR率が得られ，このため高ウイルス例の治療に対しては，PEG-IFN/RBV療法が第一選択となっている．1型では，今後，より治療効果の高いプロテアーゼ阻害薬の併用による治療が期待されるが，副作用の問題などでPEG-IFN/RBV療法の必要性も残る．2型においては，現行のPEG-IFN/RBV療法の24週間治療が最良の治療と考えられている．1型・高ウイルス例におけるPEG-IFN/RBV療法の現状，問題点，治療の予測因子，および今後の治療(PEG-IFN/RBV+プロテアーゼ阻害薬の三者併用療法)について述べる．

PEG-IFN/RBV療法の現状

2004年12月から開始されたPEG-IFN/RBV療法により，1型・高ウイルス例でもSVR率は40～50%となった．現在は，C型慢性肝炎治療の第一選択と考えられている．ここでは，当院の成績と当院も参加している九州大学が中心となって集積したKULDSのデータを用いて述べる．特にKULDSデータについては，Furusyoらにより報告された文献を参照する[1]．KULDSデータは2009年8月までに2,871例の登録があり，1型・高ウイルス例については1,152例が解析可能であった．PEG-IFN/RBV療法では，48週間治療が基本であるが，**図1**に示すように治療中のPEG-IFNやRBVの減量ではSVR率の低下は低いが，40週までに治療を中止した場合はSVR率が11%まで低下する．治療中止は，約20%にみられる．特にPEG-IFN/RBV療法の副作用による中止例は約9%である．この中止例の内約半数は，全身倦怠感やうつ症状によるものであった．また若年者でのSVR率は高いが，**図2**に示すように加齢とともに低下し，70歳以上の高齢者ではSVR率はより低くなる．高齢者では，PEG-IFNやRBVの減量者，中止例が多いが，48週間完遂例においても若年者に比べ低い．12週目までのHCV-RNAの陰性化率は約40%で終了時には約80%が陰性化するが，その後判定時

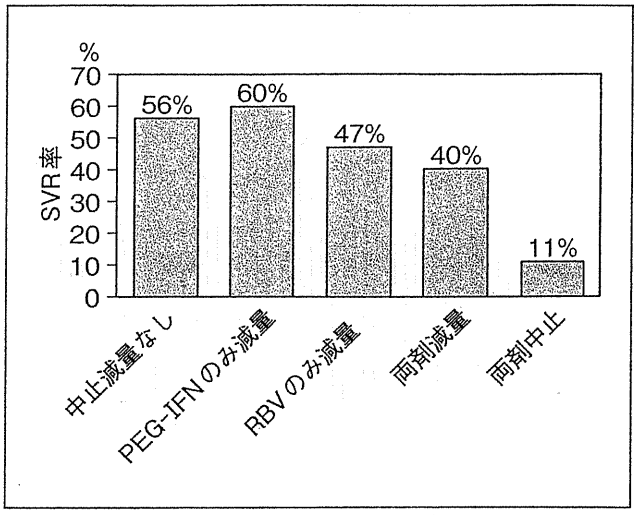

図1　1型・高ウイルス例に対するPEG-IFN/RBV服薬状況別のSVR率(n=1,152)

●C型慢性肝炎へのPEG-IFN/RBV療法のSVR率は約40～50%である.
●治療中止例では，SVR率は低い.
●SVR率は加齢とともに低下し，高齢者のSVR率は低い.

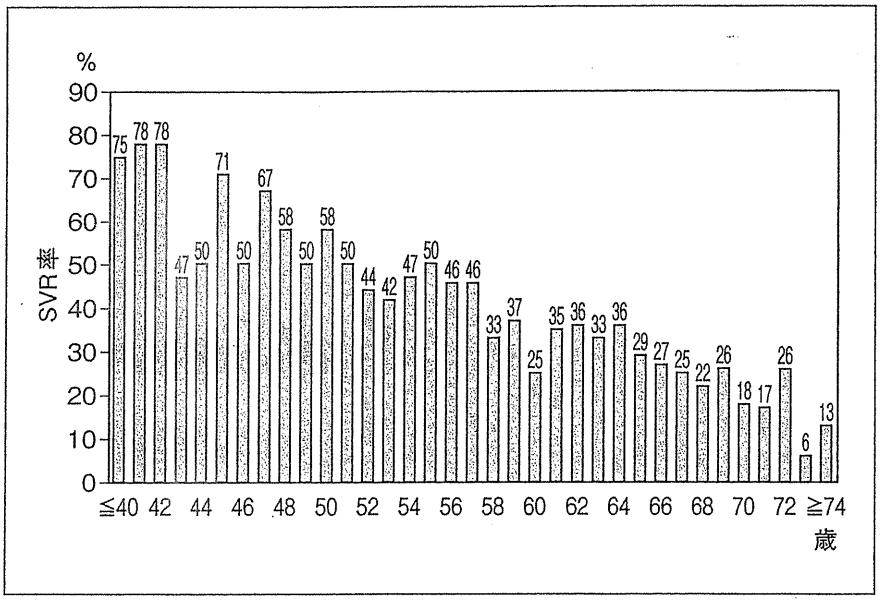

図2　年齢別の1型・高ウイルス例に対するPEG-IFN/RBV療法のSVR率
(文献1)より引用)

表1　1型・高ウイルス例へのPEG-IFN/RBV療法の問題点

① 高齢者問題
② 20～30%の高い再燃率
③ 高い中止率(うつ状態など)
④ 高額医療費
⑤ 治療効果(著効率)が40～50%
⑥ 治療期間が，48～72週と長い
⑦ 肝硬変患者への治療

(治療終了24週目)には約35%が再燃しSVR率は約40%から50%となる．治療効果は治療中のHCV-RNAの陰性化時期により異なる．4週目，8週目までにHCV-RNAが陰性化すればSVR率は97%以上となる．12週目までであれば75%となるが，13週目から36週目までにHCV-RNAが陰性化しても，48週間治療では再燃例が多くSVR率は26%と低下する．このため，現在では13週目から36週目までにHCV-RNAが陰性化したlate virological response (LVR)例に対しては，72週間治療が推奨され公費助成制度も適用されている．PEG-IFN/RBV療法の減量については，PEG-IFNは標準投与量の80%以上，RBVは60%以上の投与量があれば，標準投与例とのSVR率は差がないが，それ以下であればSVR率が低下する．特にPEG-IFNが80%以下となるとSVR率がより低下する．

2型・高ウイルス例に対しては，PEG-IFN/RBV療法の24週間投与でSVR率は83%であり，年齢差，性別の差もみられず，2型に対してはこのPEG-IFN/RBV療法が最適の治療方法と考えられている．

1型・高ウイルス例へのPEG-IFN/RBV療法の問題点(表1)●

① 高齢者のSVR率が低い，② 48週間投与では再燃率が約30%にみられる，③ 約10%に副作用中止がみられ，約半数は全身倦怠感やうつ症状である，④ 高額医療費，⑤ 治療効果が約40～50%にとどまる，⑥ 治療期間が48週間から72週間と長く，⑦ 肝硬変症例への適応がない．

◉うつ傾向患者へは，IFNβ/RBV 療法が推奨されている．
◉C 型肝炎への IFN 治療には公費助成が得られる．
◉2 型・高ウイルス例へは，24 週間の PEG-IFN/RBV 療法が最適の治療である．

②の高い再燃率については，72 週間の延長投与により LVR 例の約 50% は SVR となり，改善した．④の高額医療費については，現在医療費の公費助成制度が適用され，ほぼ改善されている．

うつ傾向の患者への IFN 治療◉

PEG-IFN/RBV 療法により C 型慢性肝炎の治療効果は改善されたが，PEG-IFNα製剤によるうつ状態の出現がみられ，うつ傾向の患者への治療は控えられている．うつ傾向の患者に対しての IFNβ/RBV 療法では，うつ傾向の悪化はみられず，SVR 率は 1 型では約 40%，2 型では 80% 以上である[2]．当院の IFN 治療 12 週目のうつ傾向のアンケート調査(BDI-Ⅱ)では，軽症の抑うつ傾向の出現率は PEG-IFN/RBV 療法では約 39%，IFNβ/RBV 療法では 9% で，有意に IFNβ/RBV が低かった．中等度以上は，PEG-IFN/RBV では 21% であったが，IFNβ/RBV ではみられなかった．現在ではうつ傾向のみられる高ウイルス例に対しては，2011 年度のガイドラインでも IFNβ/RBV 療法が推奨されている．

1 型・高ウイルス例への PEG-IFN/RBV 療法の予測因子◉

PEG-IFN/RBV 療法の予測因子としては，宿主側因子として，年齢，性，ウイルス側因子として，genotype，治療前のウイルス量，が考えられていたが，2009 年に宿主側因子として遺伝子多型(IL28B の SNPs)が発見され[3]，ウイルス側因子としても，core 70/91 のアミノ酸の置換や interferon sensitivity determing region (ISDR) の変異などが有用な因子として考えられている．IL28B の SNPs (rs8099917) の分布は，当院の 317 例では PEG-IFN/RBV 治療効果の高い major allele (TT)は 76% で，治療効果が低い minor allele (TG/GG)は 24% であった．IL28B 別の PEG-IFN/RBV 治療効果は，**図 3** に示すように IL28B の TT 群では，SVR は 58%，再燃 transient response (TR) は 34%，無効 non virological response (NVR)は 8% で，TG/GG 群では SVR は 36%，TR は 17%，NVR は 47% であった．SVR 率は TT 群が高く，一度も HCV-RNA が陰性化しなかった NVR 率は TG/GG 群が有意に高かった．

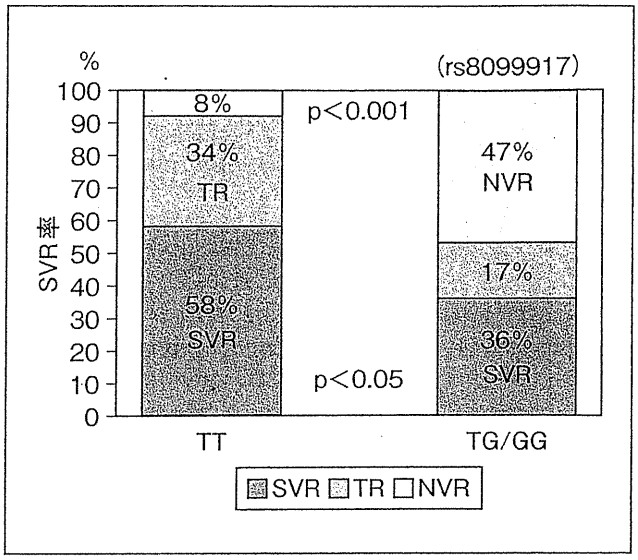

図 3　1 型・高ウイルス例に対する PEG-IFN/RBV 療法の IL28B の SNPs 別の SVR，TR，NVR の割合

PEG-IFN/RBV/telaprevir による三剤併用療法◉

1 型・高ウイルス例への 48 週間の PEG-IFN/RBV 療法では，SVR 率は約 40～50% であり，中には 72 週間と長期投与となる．治療期間の短縮と治療効果の向上を目指して，PEG-IFN/RBV 療法にプロテアーゼ阻害薬を併用する治療が検討され，2011 年中に保険適用される予定である．治療期間は 24 週間で，プロテアーゼ阻害薬としてテラプレビル telaprevir (TVR) を用い，治療開始から 12 週間は TVR を PEG-IFN/RBV に加

◉宿主側予測因子として，遺伝子多型(IL28B)が測定可能となった．
◉今後 PEG-IFN/RBV/TVR の三者併用療法が導入され，治療期間の短縮，SVR 率の向上が期待される．
◉PEG-IFN/RBV/TVR 療法不適応例へは，IFN 単独・少量・長期治療も推奨されている．

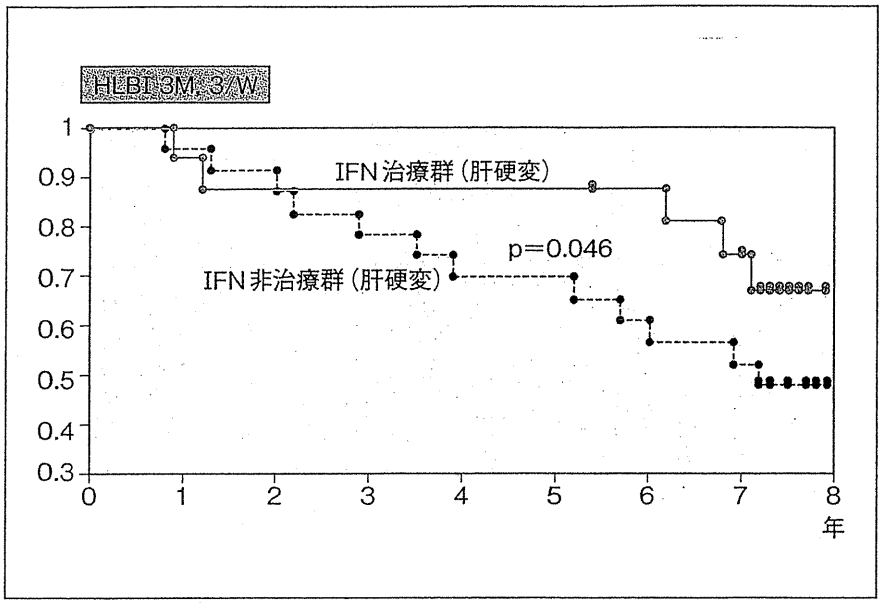

図4　1型・高ウイルス肝硬変症例に対する IFN 単独少量・長期治療の非発癌率の推移
（文献5)より改変引用）

えた三剤併用療法を行い，次の12週間は PEG-IFN/RBV 二剤併用療法を行う．臨床治験結果では，IFN 未治療者の SVR 率は70％以上で，TR 例の SVR 率は約90％で，PEG-IFN/RBV 療法に比べかなりの SVR 率の改善がみられる．特に IL28B が TT 群であれば SVR 率が非常に高く，TG/GG 群であれば，core 70 のアミノ酸置換がない wild の場合は SVR 率が高いが，mutant（置換あり）となると SVR 率が低下する[4]．つまり，PEG-IFN/RBV/TVR の三剤併用療法においても，IL28B や core 70 のアミノ酸の置換は予測因子の一つであり，IL28B（TG/GG）かつ core aa70（mutant）かつ ISDR（0-1）の場合，PEG-IFN/RBV/TVR の三剤併用療法においても治療効果はきわめて低い．

IFN 単独少量・長期療法◉

PEG-IFN/RBV 療法や PEG-IFN/RBV/TVR 療法が不適応な症例（血小板数低値，ヘモグロビン低値，肝硬変症例など）に対しては，他の治療方法で HCV-RNA の陰性化が望めない場合，肝発癌予防のために IFN 単独・少量・長期投与が推奨されている．2011年度のガイドラインでは，IFN α（human lymphoblastoid interferon：HLBI）の300万単位を週3回筋注する．なるべく自己注射を勧める．PEG-IFN α 2a を用いる場合は，1から2週間に1回90 μg を皮下注する．IFN 単独・少量・長期投与では，肝障害（AST，ALT 値高値）が改善し，AFP 値も低下する症例がみられ，肝硬変症例では3年間の治療により有意に肝発癌を抑制できる[5]（図4）．適応は，肝機能異常（AST，ALT 値高値），AFP 値高値，肝硬変症例などである．治療期間はできれば3年間以上継続することが必要である．

おわりに◉

近年C型肝炎に対する抗ウイルス療法は進化し，PEG-IFN/RBV/TVR の三剤併用療法による24週間治療で75％以上の SVR 率が可能となった．抑うつ傾向の患者へも IFN β/RBV 療法が確