Table 2. Predictive Factors for SVR in Patients with HCV Genotype 1*

Factor	Category	Odds ratio	95% CI†	p value
Period of IFN therapy (week)	4 or 6/ 8	1/8.93	2.14-37.03	0.003
AST (IU/L)	<76/≥76	1/2.17	0.85-5.55	0.102
Sex	Man / Woman	1/0.56	0.16-2.00	0.367
ALT (IU/L)	<100/≥100	1/1.67	0.47-5.93	0.430
Liver histology (fibrosis)	1 /2,3,4	1/0.79	0.39-1.60	0.507
Age (years)	<50/ ≥50	1/0.80	0.23-2.79	0.726

***ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; IFN, interferon and CI; confidence interval.**

with an internal diameter of 2 mm (Tohoku University style, Kakinuma Factory, Tokyo, Japan), fixed in 10% formalin, and stained with hematoxylin-eosin, Masson's trichrome, silver impregnation, and periodic acid-Schiff after diastase digestion. The size of specimens for examination included more than six portal areas. Histopathological interpretations of these 3-to 4-μm thick sections were made independently by experienced liver pathologists (YA and HK) who had no clinical information or knowledge of chronological order of the biopsies in each pair. The biopsy specimens were scored according to the system of Desmet et al (20).

Statistical analysis

Independent factors that might have influenced SVR were studied using the logistic regression analysis, and the following variables were evaluated as prognostic factors: sex, age, liver histology, biochemical factors (aspartate aminotransferase (AST), ALT before IFN therapy, and period of IFN therapy. Significance of trends in SVR based on periods of IFN therapy was determined Cochran-Armitage trend test. The SPSS software package (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis. A p value of <0.05 was considered to indicate a significant difference.

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase

Results

Patients' characteristics

Table 1 shows the characteristics of the 111 patients who received IFN therapy. A total of 40 patients showed HCV genotype 1 and the remaining 71 patients showed HCV genotype 2.

Efficacy of treatment

Out of 111, 64 patients (57.7%) had SVR. Based on the difference of HCV genotype, the SVR rate was 47.5% (19/40) in genotype 1 and 63.3% (45/71) in genotype 2. We then investigated the factors associated with SVR after termination of IFN. Univariate analysis in patients with genotype 1 identified the following one factor that influenced SVR when the period of IFN treatment was 8weeks (Table 2). As one factor was associated with SVR, we did not evaluate the multivariate analysis.

On the other hand, univariate analysis in patients with genotype 2 did not identify the factor that influenced SVR (Table 3). In genotype 2, the SVR in patients treated with

Table 3. Predictive Factors for SVR in Patients with HCV Genotype 2 *

Factor	Category	Odds ratio	95% CI†	p value
AST (IU/L)	<76 /≥76	1/2.21	0.80-6.14	0.126
Sex	Man / Woman	1/0.61	0.22-1.64	0.324
Period of IFN therapy (week)	4 or 6/ 8	1/1.63	0.57-4.69	0.361
ALT (IU/L)	<100/≥100	1/1.22	0.41-3.57	0.721
Age (years)	<50/ ≥50	1/0.80	0.23-2.79	0.726
Liver histology (fibrosis)	1 /2,3	1/0.88	0.54-1.70	0.876

***ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; and IFN, interferon and CI; confidence interval.**

Table 4. SVR Based on HCV Genotype and Administration Period of Interferon

HCV genotype	Administration period (week)		
	4W	6W	8W
Genotype 1 †	0% (0/6)	33.3% (5/15)	73.7% (14/19)
Genotype 2 † ‡	40% (2/5)	60% (9/15)	66.7% (34/51)

***HCV indicates hepatitis C virus; and SVR, sustained virological response.**
† p <0.001 in genotype 1, p =0.32 in genotype 2 by Cochran-Armitage method
‡ Three patients had HCV genotype 2b. These three patients were treated for 8 weeks and all the patients showed SVR. Remaining patients had genotype 2a.

the 8-week regimen was similar statistically to that in patients treated with the 4- or 6-week regimen.

Table 4 shows the SVR based on the HCV genotype and period of IFN therapy. According to Cochran-Armitage method, the 8-week IFN therapy regimen was the best in order to eradicate HCV RNA in genotype 1. On the other hand, in genotype 2, the 6-week regimen was almost the same as the 8-week regimen.

Adverse events

Within one week after the initiation of treatment, flu-like symptoms appeared in all the patients. Pain in the joints or muscle occurred in 50 cases. However, none of the patients withdrew from this treatment due to IFN-related side effects.

Discussion

We have described the efficacy of short-term IFN-beta therapy for chronic hepatitis C patients with low virus load. The present study was limited by a retrospective cohort trial. However, several findings from the present study have direct implications for the short-term IFN treatment of CH patients with low virus load. First, HCV RNA was cleared in more than 50% patients. Second, no patients withdrew from the treatment due to IFN-related side effects. Okanoue et al reported that side effects occurred when the daily IFN dose was increased (21). However, in the 8-week study period, there were no serious side effects. Third, the 8-week regimen of IFN therapy was preferable to eradicate HCV RNA compared to the 4 or 6-week regimen in genotype 1. On the other hand, in genotype 2, SVR by the 6-week regimen of IFN therapy was not significantly different from SVR by the 8-week regimen. These results indicate that 1) in patients with genotype 1 and low virus load, the 8-week regimen of IFN was recommended as the first treatment, 2) in patients with genotype 2 and low virus load, the 6-week regimen of IFN was recommended as the first treatment. This result is likely in agreement with several previous clinical trials (22-26).

In patients with genotype 1b and a high load of HCV-RNA, the clearance rate of HCV-RNA is less than 10% by the usual 6-month course of IFN monotherapy. In these IFN-resistant patients, the eradication rate of HCV-RNA level is at most 20-50% by the latest prolonged IFN therapy, combination therapy of IFN/ribavirin or pegylated IFN administration.

At present, combined IFN and ribavirin therapy is the standard therapy for chronic hepatitis C patients with genotype 1b and a high load of HCV-RNA. Next, in our hospital SVR of the 24-week IFN regimen in patients with a low load of HCV-RNA was 50.9% (220/432) in genotype 1b, 79.9% (279/349) in genotype 2a, and 71.4% (45/63) in genotype 2b. These results indicate that SVR of the 24-week regimen was higher than that of the short term regimen in genotype 2. However, prolonged IFN therapy is often associated with various side effects. A lower total dose and shorter administration period of IFN would be preferable in terms of both cost and safety.

Fortunately, patients with low HCV-RNA levels tend to eradicate HCV RNA with a low dose of IFN. The present study indicates that short-term IFN-beta therapy has no severe side effects. Thus, short-term IFN therapy is recommended for the patients who tend to have a SVR and have IFN- induced adverse events.

Conclusion

We think that the 6 or 8-week regimen of IFN-beta therapy is one therapy selection for chronic hepatitis C patients who tend to have a SVR and have IFN-induced adverse events.

Acknowledgement

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分担研究報告書

C型肝炎に対するPeg-IFN/Ribavirin併用療法における貧血予測
-治療中の高度貧血予測アルゴリズムの構築-

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研究要旨：大阪大学を含む当研究班の６施設にて Peg-IFN/Ribavirin 併用療法を施行した Genotype1 型高ウイルス量Ｃ型肝炎症 1501 例 を対象とし、データマイニング手法を用いて、PegIFN/ Ribavirin 併用療法における治療中の高度貧血（Hb8.5g/dl 未満）予測アルゴリズムの構築を試みた。データマイニング解析は、対象症例を、モデル作成群とモデル検証群の２：１に分け、モデル作成群にてアルゴリズムを構築し、検証群との比較を行った。モデル作成群にて構築した高度貧血の予測アルゴリズムにおける説明因子は、治療前 Hb、Ccr、治療開始２週時Hb減少量であった。治療前Hb14g/dl未満の症例では、Ccr 80ml/min未満の症例で11.8%、Ccr 80ml/min 以上で治療開始２週時 Hb 減少量が 2g/dl 以上の症例で11.5%と、ともに高率に高度貧血を認めた。この予測アルゴリズムによるモデル検証群における結果との相関係数は 0.96 と非常に良好であった。また、判別効率曲線による評価においても、本研究にて作成した高度貧血予測モデルの判別効率は高く、安定性にも優れているものと考えられた。

A.　研究目的

データマイニング手法を用いて、Genotype1 型　高ウイルス量Ｃ型肝炎に対する PegIFN/ Ribavirin 併用療法における治療中の高度貧血（Hb8.5g/dl 未満）予測アルゴリズムを構築することを目的とした。

B.　研究方法

大阪大学を含む当研究班の６施設にて Peg-IFN/Ribavirin 併用療法を施行した Genotype1 型高ウイルス量Ｃ型肝炎症 1501 例を対象とした。研究方法は、予備解析としてデータ欠損率 15%以上の項目は除外して、高度貧血（ Hb8.5 g/dl 未満）に関連する因子の傾向分析を行い、有意であった因子について、データマイニング解析を行った。データマイニング解析は、対象症例を、乱数表を用いたランダムサンプリングにて、モデル作成群とモデル検証群の２：１に分け、モデル作成群にてアルゴリズムを構築し、検証群との比較を行った。また、モデルの効率性は、判別効率曲線によっての評価し、検証群における判別効率分析の結果と比較した。

本研究にて検討した因子は、年齢、性別、BMI、肝組織所見（Activity、Fibrosis）、治療前血液検査（Hb、WBC、Plt、TP, Alb, Cr, AST, ALT, γGTP, T.Chol, HDL-Chol, LDL-Chol, TG, FBS, AFP）、ｸﾚｱﾁﾆﾝｸﾘｱﾗﾝｽ(Ccr)、HCVRNA 量、治療因子（PegIFN 投与量, RBV 投与量）、治療開始後の血球減少量（1, 2, 4, 8 週目）であった。このうち、肝組織所見（Activity、Fibrosis）は 21%のデータ欠損、治療開始後の血球減少量（1 週目）は 16%のデータ欠損があったため、検討から除外した。

C.　研究結果

１）全症例における高度貧血率は 4.5%であっ

た。傾向分析にて、高度貧血に関係する有意な因子は、年齢、性別、Hb、Ccr、治療開始後の血球減少量（2，4週）の6因子であった。

2）データマイニング解析の対象は、予備解析で有意な上記6因子の全てのデータを有し、PegIFN、RBV を標準投与量にて開始した 1082 例(モデル作成群　692 例、モデル検証群 390 例)とした。

3）モデル作成群にて構築した高度貧血(Hb8.5g/dl)の予測アルゴリズムを図1に示す。説明因子は、治療前 Hb、Ccr、治療開始2週時 Hb 減少量であった。治療前 Hb14g/dl 以上の症例では、高度貧血例は少なく、次の説明因子である治療開始 2 週時 Hb 減少量が 2g/dl 以上でも、高度貧血率は 2.5%であったが、治療前 Hb14g/dl 未満の症例では、Ccr 80ml/min 未満の症例で 11.8%、Ccr 80ml/min 以上で治療開始2週時 Hb 減少量が 2g/dl 以上の症例で 11.5%と、ともに高率に高度貧血の出現を認めた。また、この予測アルゴリズムをモデル検証群に当てはめた結果、相関係数は 0.96 と非常に良好な相関がみられた。

4)判別効率曲線によりモデルの効率性と安定性を評価した。貧血発現率の高い順にグループを並び替え、累積症例数(%)と同定された貧血症例の累積（%）との関連をみたものであるが、モデル作成群の曲線は、基準線に比し左上方に位置し、判別効率は高いものであり、さらにモデル検証群の曲線とも非常に近似しており、安定性にも優れていた。

D.　考察

治療中に Hb8.5g/dl 未満の高度貧血をきたす症例を予測するアルゴリズムを構築し、治療前 Hb、Ccr、治療開始後 2 週時 Hb 減少量が説明因子として同定された。この高度貧血予測アルゴリズムは、治療前 Hb が 14g/dl 未満で、Ccr が 80ml/min 未満の症例、および Ccr が 80ml/min 以上でも治療開始後 2 週時点で Hb が 2g/dl 以上減少する症例は貧血進行による中止のリスクが高いことを示している。

我々は、Ribavirin の副作用である溶血性貧血による薬剤中止予測について、治療開始 2 週後の Hb 減少度（2g/dl）が重要であり、治療開始 2 週時に Hb2g/dl 低下した時点での Ribavirin　200mg 減量が有用であることを報告してきた（Two by Two rule)。特に、Ribavirin の全身クリアランスを反映する CL/F が低値である症例では貧血中止が高率であったが、本研究の結果は、網羅的な解析の中で同様の結果が得られたものと考えられた。

E.　結論

データマイニング手法を用いて、Genotype1 型高ウイルス量 C 型肝炎に対する PegIFN/Ribavirin 併用療法における治療中の高度貧血予測のアルゴリズムを構築した。

F.　研究発表

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G. 知的所有権の出願・登録状況

(ア) 特許取得：なし

(イ) 実用新案登録：なし

(ウ) その他：なし

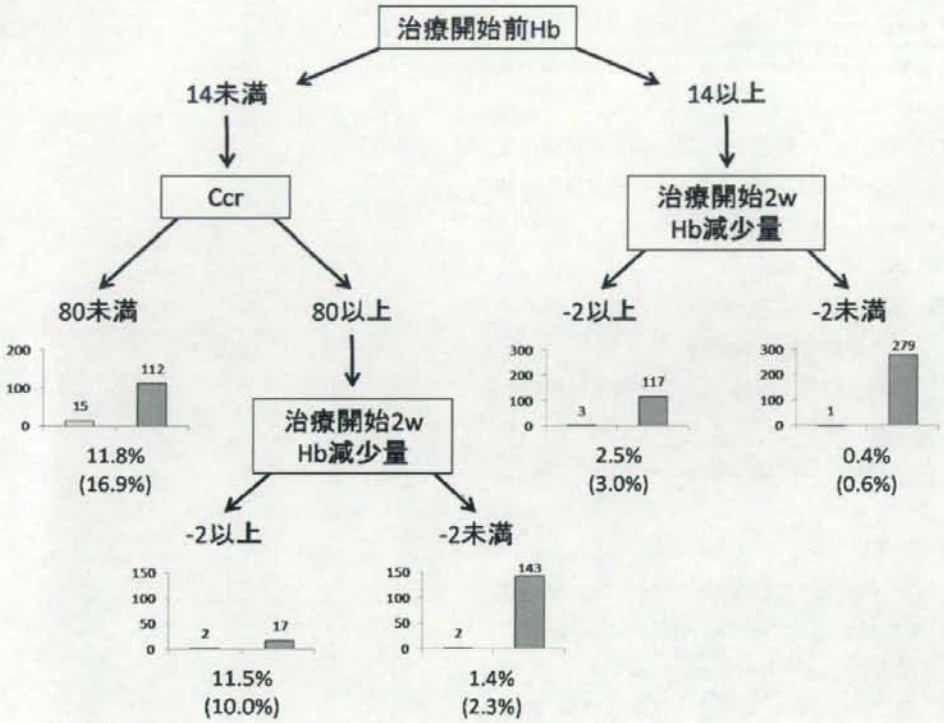

図１．モデル作成群における高度貧血(Hb8.5g/dl)の予測アルゴリズム

（ ）内%はモデル検証群における高度貧血率

■Hb8.5g/dl 以上　■Hb8.5g/dl 未満

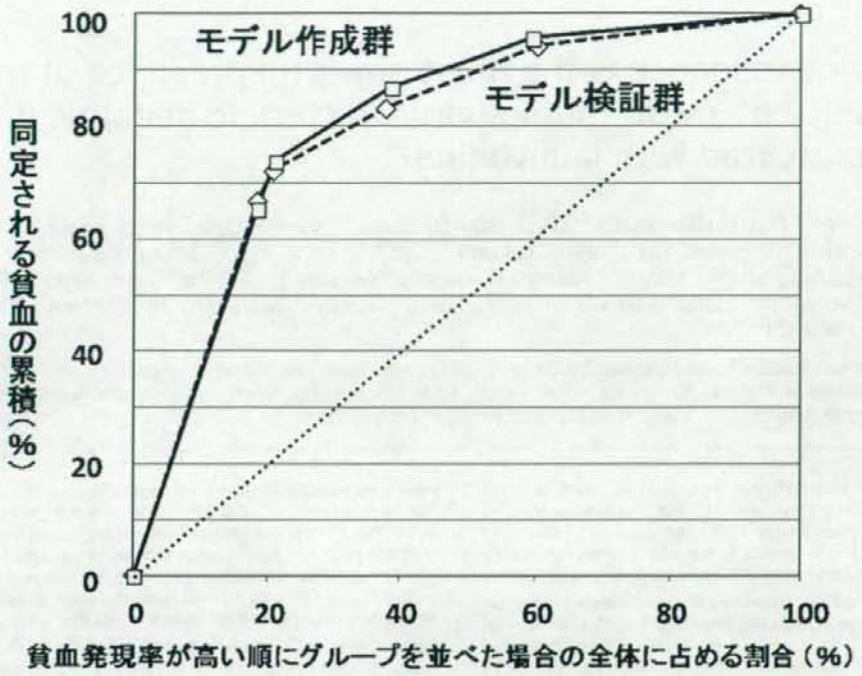

図２．判別効率の比較による高度貧血予測モデルの判別公立効率ならびに安定性評価

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Original Article

Initial viral response is the most powerful predictor of the emergence of YMDD mutant virus in chronic hepatitis B patients treated with lamivudine

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Aim: Lamivudine (LAM) has been widely used to treat chronic hepatitis B (CHB) patients, but the emergence of a LAM-resistant virus greatly limits its therapeutic efficacy. In this study, we tried to identify factors affecting the emergence of a LAM-resistant virus in CHB patients treated with LAM.

Methods: The subjects were 190 CHB patients in continuous LAM therapy (139 males, mean age 50 years, 87 HBeAg-positive). The mean duration of follow-up was 39 months (range 12–104). The initial viral response (IVR) was defined as HBV DNA < 4.0 logcopies/mL, and the initial biochemical response (IBR) as normalization of alanine aminotransferase (ALT) (<40 IU/L) at 6 months.

Results: IVR was positive in 86% of the patients. The cumulative emergence rates of LAM-resistant virus were 10% at 1 year, 30% at 2 years and 46% at 3 years. In univariate analysis, factors contributing to the emergence of LAM-resistant virus were baseline HBV DNA > 6.5 logcopies/mL ($P = 0.0044$), HBeAg-positivity ($P = 0.0062$), IBR ($P = 0.01$) and IVR ($P < 0.0001$). The cumulative emergence rates of LAM-resistant virus in IVR-positive and -negative patients were 4% and 41% at 1 year, and 41% and 79% at 3 years. In multivariate analysis, only IVR was an independent factor affecting the emergence of LAM-resistant virus ($P < 0.0001$).

Conclusion: IVR is a useful factor for predicting the emergence of LAM-resistant virus in CHB patients treated with LAM. For IVR-negative patients, therapeutic options other than LAM monotherapy should be used because of the high incidence of the emergence of LAM-resistant virus.

Key words: chronic hepatitis B, initial viral response, lamivudine monotherapy, lamivudine-resistant virus

INTRODUCTION

MORE THAN 350 million people are chronically infected with hepatitis B virus (HBV) worldwide.[1] Chronic HBV infection eventually leads to the development of cirrhosis and hepatocellular carcinoma (HCC), and raises the risk of hepatic disease-related death. Nucleos(t)ide analogs are widely used to suppress HBV replication and the progression of HBV-related liver diseases. Lamivudine (LAM), the first approved nucleoside analog for chronic HBV infection, has been shown to suppress viral replication and disease activity.[2] In addition, LAM therapy has recently been reported to reduce the incidence of HCC, the risk of major complications and to improve survival.[3,4] However, the relatively high incidence of LAM resistance is a serious problem in the case of LAM therapy for chronic HBV infection. The emergence of LAM-resistant HBV is linked to the reappearance of active viral replication, followed by the worsening of liver disease.

LAM-resistant HBV is based on point mutation within the YMDD motif of the reverse transcriptase domain of

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HBV (YMDD mutation).[5,6] The emergence rates of the mutant virus have been reported to be 24% at 1 year and 70% at 4 years from the start of treatment.[7]

Recent work has shown that newly developed nucleos(t)ide analogs, such as adefovir dipivoxil (ADV) and entecavir (ETV), are also useful agents for controlling patients with chronic HBV infection.[8–11] In particular, the drug-resistant mutant virus has been reported to appear less frequently in cases of treatment with ADV and ETV than with LAM.[12,13] For this reason, LAM has been replaced by ADV and ETV for the treatment of chronic hepatitis B. However, there are still a considerable number of patients with chronic HBV infection who are already on continuous LAM therapy. Thus, further clarification is needed of what factors influence the emergence of the LAM-resistant HBV in LAM treatment for chronic HBV infection.

For a more precise evaluation, we investigated baseline and on-treatment factors affecting the emergence of LAM-resistant mutant virus in patients with chronic hepatitis B treated with LAM.

METHODS

Patients and treatment

THIS STUDY WAS conducted at nine institutions in the Osaka area of Japan (Osaka Police Hospital, Osaka Minami Medical Center, Osaka Kouseinenkin Hospital, Osaka Rousai Hospital, Kinki Central Hospital, Ikeda City Hospital, Osaka National Hospital, Otemae Hospital and Osaka University Hospital). The subjects were 190 consecutive patients with chronic hepatitis B who underwent continuous LAM therapy for more than 12 months. All patients tested positive for hepatitis B surface antigen (HBsAg) or had detectable levels of HBV DNA in their sera by the polymerase chain reaction (PCR)-based method (for 100 patients)[14] or the transcription-mediated amplification (TMA) method (for 90 patients).[15] Exclusion criteria were patients with antihepatitis C antibody, antihuman immunodeficiency virus antibody and other forms of liver diseases (alcoholic liver disease, drug-induced liver disease and autoimmune hepatitis). Forty-one (22%) patients had previously received interferon (IFN)-α therapy for 24 weeks.

All patients were treated with 100 mg of LAM daily. After the beginning of the therapy, liver function tests and HBV DNA were measured every other month for the first 6 months and every two months thereafter. HBeAg and anti-HBe were tested every 6 months. In 33 patients (18%), combination therapy with IFN was carried out for the initial 6 months. Three or six megaunits of natural IFN-á were administered daily for the first 2 weeks and three times a week thereafter, followed by LAM monotherapy. The mean follow-up period of the 190 patients was 39 (range 12–104) months. The LAM-resistant YMDD mutant virus was detected by the PCR-enzyme-linked minisequence (ELMA) assay[16] when the virological or biochemical breakthrough was observed. The YMDD mutant virus was found in 86 (45%) patients during follow-up. Fifty-eight of these patients underwent ADV therapy in addition to ongoing LAM treatment and were excluded from the follow-up when ADV administration began. In this study, the initial viral response (IVR) was defined as HBV DNA < 4.0 logcopies/mL, and the initial biochemical response (IBR) as normalization of alanine aminotransferase (ALT) (<40 IU/L) after 6 months of therapy.

Table 1 Patient characteristics

Gender (male/female)	139/51
Age (years)	50 ± 11
Chronic hepatitis/liver cirrhosis	113/77
Hepatocellular carcinoma	14 (7%)
AST (IU/L)	122 ± 157
AST (IU/L)	177 ± 236
ALT (≤1/1–2/2–5/>5 × ULN)	22/53/65/50
Platelet (10^4/mm^3)	12.6 ± 5.1
Prothrombin time (%)	71.5 ± 16.6
HBV DNA (logcopies/mL)	6.5 (3.0–7.6<)
HBeAg (positive/negative)	87/103
Combination with interferon	33 (17%)
Duration of treatment (months)	38.9 ± 17.5

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ULM, upper limit normal.

The patients' clinical characteristics are shown in Table 1. There were 139 males and 51 females, ranging in age from 25 to 75 (mean 50) years. Of them, 113 (59%) patients were diagnosed as having chronic hepatitis and the remaining 77 patients (41%) as having cirrhosis according to liver histology and/or the imaging procedure. HCC was developed in 14 (7%) patients. The aspartate aminotransferase (AST) at baseline was 122 ± 157 IU/l, and the ALT at baseline was 177 ± 236 IU/L. Abnormal ALT was observed in 168 (88%) patients. Eighty-seven patients (46%) tested positive for HBeAg. The median HBV DNA at baseline was 6.5 (range 3.0 to 7.6<) logcopies/mL.

HBV testing

HBsAg, hepatitis B e antigen (HBeAg) and antihepatitis B e antibody (anti-HBe) were examined by chemiluminescent immunoassay or enzyme immunoassay.

The HBV DNA level was measured by the PCR-based method (Amplicor HBV monitor; Roche Diagnostics, Tokyo, Japan)[14] or the TMA method (TMA-HPA; Fujirebio, Tokyo, Japan),[15] which have lower detection limits of 2.6 and 3.7 logcopies/mL, respectively. The LAM-resistant YMDD mutant virus was examined by the PCR–ELMA method.[16]

Statistical analysis

Comparisons of categorical and continuous variables between groups were done by the χ^2-test, Student's *t*-test and Mann–Whitney's *U*-test. The cumulative emergence rates of LAM-resistant virus were evaluated with the Kaplan–Meier's curve and the differences between groups were analyzed by the log-rank test. For multivariate analysis to investigate factors affecting the cumulative emergence rate of LAM-resistant virus, Cox proportional hazard regression analysis was carried out. A *P*-value of less than 0.05 (two-tailed) was considered to be statistically significant.

RESULTS

Therapeutic efficacy and the emergence of LAM-resistant mutant virus

AMONG THE 190 patients with chronic hepatitis B who underwent continuous LAM therapy, reduction of HBV DNA to less than 4 logcopies/mL was observed in 86% (163/190) at 6 months, 89% (151/170) at 1 year, 88% (83/94) at 2 years and 89% (48/54) at 3 years of the treatment. Normalization of ALT was achieved by 77% (146/190) at 6 months, 83% (141/170) at 1 year, 81% (76/94) at 2 years and 83% (45/54) at 3 years. Among the 87 HBeAg-positive patients, HBeAg was cleared in 22% (19/86) at 6 months, 26% (21/80) at 1 year, 22% (11/50) at 2 years and 43% (16/37) at 3 years. As for the virological and biochemical response at 6 months of therapy, 163 (86%) of the patients achieved IVR, whereas IBR was seen in 146 (77%) of patients.

When the various patient characteristics were compared between IVR-positive and -negative patients (Table 2), HBV DNA at baseline tended to be lower in patients showing IVR (median 6.5 [range 3.0 to 7.6<] logcopies/mL) than in those who did not show IVR (median 7.3 [range 4.3 to 7.6<] logcopies/mL) ($P < 0.0001$). IVR-negative patients had higher HBeAg positivity at baseline than IVR-positive patients (81% vs 40%, $P = 0.01$). As for the emergence of LAM-resistant mutant virus during follow-up, it was detected more frequently in IVR-negative patients (21/27, 78%) than in IVR-positive patients (65/163, 40%) ($P = 0.002$).

Among the 190 patients examined in this study, the emergence of LAM-resistant YMDD mutant virus occurred in 86 (45%) patients during follow-up. The cumulative probabilities of the emergence of the YMDD mutant virus were 10% at 1 year, 30% at 2 years and 46% at 3 years.

Factors affecting the emergence of LAM-resistant mutant virus

Factors affecting the cumulative probability of the emergence of the YMDD mutant virus were investigated using

Table 2 Comparison of patient characteristics between IVR-positive and -negative patients

	IVR ($n = 163$)	Non-IVR ($n = 27$)	*P*-value
Gender (male/female)	118/45	21/6	NS
Age (years)	50 ± 11	48 ± 12	NS
Chronic hepatitis/liver cirrhosis	91/72	22/5	NS
Hepatocellular carcinoma	13 (8.0%)	1 (4%)	NS
AST (IU/L)	131 ± 167	69 ± 34	NS
ALT (IU/L)	190 ± 252	100 ± 55	NS
ALT (≤1/1–2/2–5/>5 × ULN)	21/43/52/47	1/10/13/3	NS
HBV DNA (logcopies/mL)	6.5 (3.0–7.6<)	7.3 (4.3–7.6<)	<0.0001
HBeAg (positive/negative)	65/98	22/5	0.01
Combination with interferon	27 (17%)	6 (22%)	NS
Emergence of LAM-resistant viruses	65 (40%)	21 (78%)	0.002
Duration of treatment (months)	39.2 ± 17.2	37.3 ± 19.1	NS

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IVR, initial viral response; LAM, lamivudine; NS, not significant; ULN, upper limit normal.

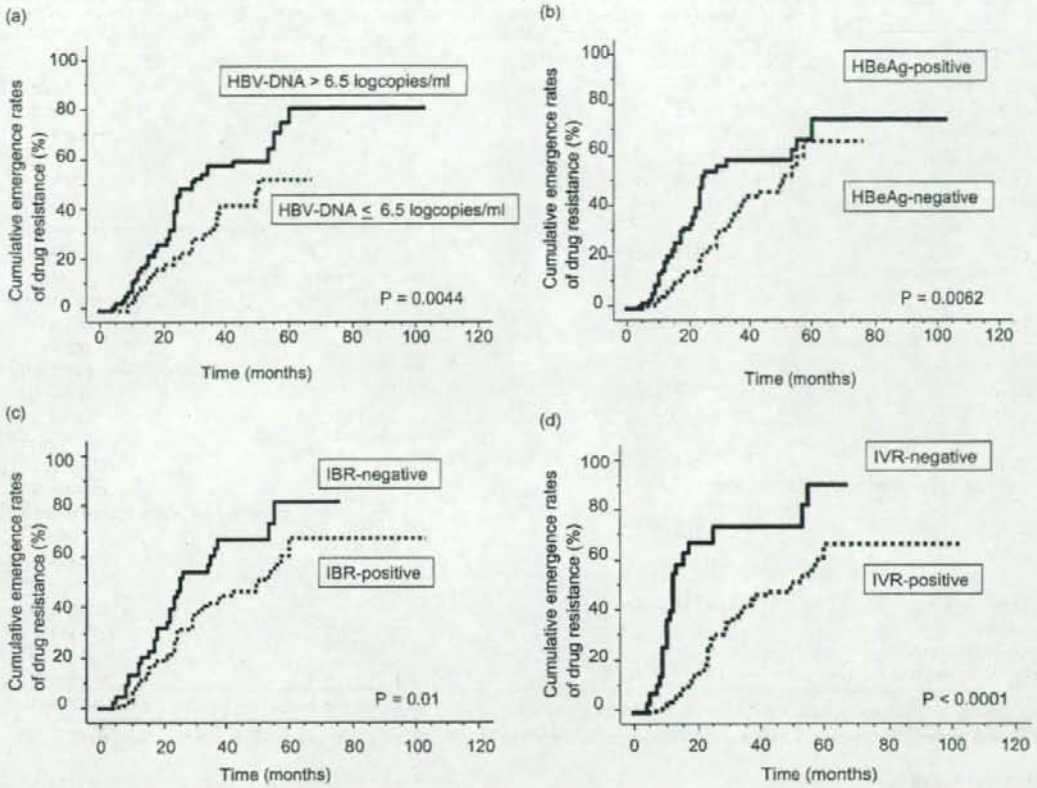

Figure 1 Cumulative emergence rate of lamivudine (LAM)-resistant virus in patients with chronic hepatitis B virus (HBV) infection treated with LAM according to: (a) HBV DNA at baseline; (b) hepatitis B e antigen (HBeAg) status; (c) the presence or absence of initial biochemical response (IBR); and (d) the presence or absence of initial viral response (IVR).

both univariate and multivariate analyses. Nine baseline and on-treatment factors – gender, age, liver disease (chronic hepatitis or cirrhosis), ALT at baseline, HBeAg positivity, HBV DNA at baseline, combination therapy with IFN-α, presence of IBR and presence of IVR – were examined. The cumulative emergence of LAM-resistant virus was significantly higher in patients with baseline HBV DNA > 6.5 logcopies/mL than in those with HBV DNA ≤ 6.5 logcopies/mL ($P = 0.0044$) (Fig. 1a). HBeAg-positive patients revealed a significantly higher emergence rate of the LAM-resistant virus than HBeAg-negative patients ($P = 0.0062$) (Fig. 1b). A significant difference was also seen in the cumulative emergence of the YMDD mutant virus between IBR-positive and -negative patients ($P = 0.01$) (Fig. 1c). Furthermore, the cumulative emergence of LAM-resistant mutant virus was much higher in the IVR-negative patients than in the IVR-positive patients ($P < 0.0001$) (Fig. 1d). The cumulative emergence rates of LAM-resistant virus in the IVR-positive and -negative patients were 4% and 41% at 1 year, 25% and 69% at 2 years, and 41% and 79% at 3 years, respectively. Gender, age, liver disease, ALT at baseline and combination therapy of IFN-α did not show a significant relation with the emergence of the YMDD mutant virus. When factors influencing the higher cumulative emergence of LAM-resistant virus were searched for by multivariate analysis, only the absence of IVR was selected as a significant independent factor ($P < 0.001$) (Table 3), with high HBV DNA, HBeAg positivity and the absence of IBR not being selected.

Table 3 Factors associate with emergence of LAM-resistant virus determined by multivariate analysis

	Hazard ratio	95% confidence interval	*P*-value
Gender			
0: male	1	0.497–1.455	0.55
1: female	1.176		
Age			
0: ≤50	1	0.640–1.700	0.87
1: >50	0.959		
Chronic hepatitis/liver cirrhosis			
0: CH	1	0.656–1.740	0.79
1: LC	0.935		
Pretreatment ALT (IU/L)			
0: ≤200	1	0.605–1.818	0.87
1: >200	0.953		
HBV DNA (logcopies/mL)			
0: ≤6.5	1	0.394–1.125	0.13
1: >6.5	1.502		
HBeAg			
0: negative	1	0.499–1.337	0.42
1: positive	1.225		
Combination therapy with interferon			
0: no	1	0.410–1.303	0.29
1: yes	1.368		
IBR			
0: positive	1	0.483–1.312	0.37
1: negative	1.256		
IVR			
0: positive	1	0.159–0.536	<0.001
1: negative	3.425		

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IBR, initial biochemical response; IVR, initial viral response; LAM, lamivudine.

DISCUSSION

IN LAM THERAPY for patients with chronic HBV infection, the emergence of a LAM-resistant YMDD mutant virus is a serious problem, because it inevitably restricts the antiviral efficacy of LAM. To resolve this, detailed studies are needed to identify factors related to the emergence of the YMDD mutant virus. To date, a few investigators have suggested male gender, advanced age, high baseline ALT, the presence of severe acute exacerbation of the liver disease, high baseline HBV DNA and HBeAg-positivity as possible predictors of the emergence of LAM-resistant virus.[7,17,18] Lower body surface area was also reported as a significant factor for virological and biochemical therapeutic effect.[19] In the present study, we studied 190 patients with chronic hepatitis B treated with LAM and investigated baseline and on-treatment factors affecting the emergence of LAM-resistant mutant virus. Univariate analysis revealed that two baseline factors, high HBV DNA and HBeAg positivity, had a relation to the high incidence of the YMDD mutant virus, which is consistent with previous reports.[7,17,18] In addition, two on-treatment factors, IBR and IVR, were found to be correlated with the emergence of LAM resistance. Patients who did not show IVR had a 3.4-fold higher incidence of the emergence of the YMDD mutant virus than those who did show IVR. This agrees with a previous report that the HBV DNA level after 6 months of therapy may be a determinant for subsequent occurrence of a LAM-resistant mutant virus.[20] Multivariate analysis showed that only the absence of IVR was a significant factor contributing to the emergence of LAM-resistant virus. Baseline HBV DNA and HBeAg status were not selected as significant factors by multivariate analysis probably because of the tendency for higher HBV DNA and high frequency of HBeAg positivity in IVR-negative patients compared with IVR-positive patients. It is particularly interesting that the absence of IVR, rather than other baseline and on-treatment factors, was a powerful independent pre-

dictor for the emergence of the YMDD mutant virus in LAM therapy for chronic HBV infection. This means that IVR of an on-treatment factor is very important for good therapeutic effect and the stage for the next therapeutic strategy can thus be set in a new light with this information.

Our results showed that approximately one-seventh of the patients with chronic hepatitis B treated with LAM did not achieve IVR. In the non-IVR patients, the antiviral therapeutic regimen should be amended due to the frequent emergence of LAM-resistant virus. Recently, new nucleos(t)ide analogs have become available for the treatment of chronic HBV infection. ETV has been reported to be more effective for the reduction of HBV DNA and the less frequently induced drug-resistant mutant virus than LAM in "naïve" patients with chronic hepatitis B who had not previously received nucleos(t)ide analog therapy.[10,11] ETV was also effective in patients with chronic HBV infection showing LAM resistance,[21] but the emergence rate of the ETV-resistant virus was considerably higher in LAM-resistant patients than in naïve patients.[13,22] This is because the ETV-resistant HBV strain is established by LAM-resistant YMDD mutation plus additional mutation(s) at the amino acid position(s) 184, 202 and/or 250 within the reverse transcriptase domain of HBV.[22] According to these findings, switching from LAM to ETV may be useful for treating patients who do not achieve IVR on LAM administration. This should be done before the emergence of LAM-resistant YMDD mutant virus so as not to reduce the therapeutic efficacy of ETV. In clinical practice, there are still a number of patients who have already been on continuous LAM therapy, although the current first choice drug for patients with chronic HBV infection is ETV. In our opinion, foregoing patients without IVR or YMDD mutant viruses should be switched from LAM to ETV. The therapeutic efficacy of switching from LAM to ETV in non-IVR patients should be assessed by further study with a larger number of patients.

ADV and tenofovir disoproxil fumarate (TDF) have also been shown to exert antiviral efficacy in patients with chronic HBV infection with less frequent occurrence of drug-resistant mutant virus compared to LAM.[23] In addition, unlike the case of ETV, both ADV and TDF are known to be effective in LAM-refractory patients with chronic hepatitis B, as well as naïve patients.[23] Using ADV and TDF may be helpful for the treatment of non-IVR patients, especially after the establishment of LAM-resistant mutant virus.

In conclusion, our findings indicate that IVR may be a useful factor for predicting the emergence of LAM-resistant mutant virus in patients with chronic HBV infection treated with LAM. For patients who do not achieve IVR, therapeutic options other than LAM monotherapy should be promptly implemented because of the high incidence of the subsequent emergence of the YMDD mutant virus.

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C型慢性肝炎治療の変遷

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総 説

C型慢性肝炎治療の変遷

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要旨：C型慢性肝炎に対する抗ウイルス療法は，1990年代のインターフェロン単独療法の時代から，経口抗ウイルス薬であるリバビリンの併用により飛躍的な進歩を遂げている．さらにペグインターフェロンとリバビリンの併用により，難治性であるgenotype1型高ウイルス量の症例におけるウイルス排除率は50%を超えた．さらなる治療効果の向上を目指した新規抗ウイルス剤（プロテアーゼ阻害剤，ポリメラーゼ阻害剤など）の開発も進んでおり，大規模臨床試験の結果が期待される．

索引用語：chronic hepatitis C，interferon，ribavirin，pegylated interferon plus ribavirin combination therapy，NS3 serine protease inhibitor

はじめに

C型肝炎ウイルス（HCV）は，1989年，米国のChooらによって発見された[1)]．従来，非A非B型肝炎と診断されていた患者の9割以上，アルコール性肝障害と診断されていた症例の半数以上がHCVによる肝障害であることが明らかとなり，現在，HCVキャリアは全世界で1億7000万人，本邦で約170万人と推定されている[2)]．HCV感染が一旦成立すると，健康成人への感染であっても，急性の経過で治癒するものは約30%であり，感染例の約70%でHCV感染が持続し，慢性肝炎へと移行する．慢性化した場合，ウイルスの自然排除はまれであり（年率0.2%），HCV感染による炎症の持続により肝線維化が惹起され，20～30年の経過で肝硬変や肝細胞癌が発生する[3)]．肝線維化の進展度からみた肝癌の発生率は，F0～F1で年率0.5%，F2で1～2%，F3で3～5%，F4では7%程度である[4)]．

本稿では，C型慢性肝炎治療の変遷として，インターフェロン（interferon：IFN）治療の進歩をreviewし，さらに，現在，最も治療効果の高い最新の治療として，ペグインターフェロン（pegylated IFN：Peg-IFN）/リバビリン（Ribavirin）併用療法について，大阪大学を中心としたosaka liver forum（OLF）参加施設における多施設共同研究の検討結果を紹介する．また，最も開発が進んでいる新たな治療薬剤として，NS3-4A protease阻害剤を中心に最近の知見について紹介する．

I IFN治療の端緒

C型肝炎に対するIFN治療は，1986年，Hoofnagleらが，非A非B型肝炎に対してヒト組み換えIFNαを投与し，transaminaseの正常化を確認したことに始まる[5)]．その後，ウイルス検出法（PCR法）の開発により，IFN治療により炎症が鎮静化するような症例では血中HCV-RNAが陰性化することが明らかになった[6)]．C型肝炎に対するIFN治療の臨床応用は，欧米で1991年，本邦では1992年から始まった．

IFNの治療効果は，当初は著効，再燃，無効が約1/3ずつとされたが，後にこのような治療効果にウイルス側因子が強く関与することが明らか

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Development of antiviral therapy for patients with chronic hepatitis C

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