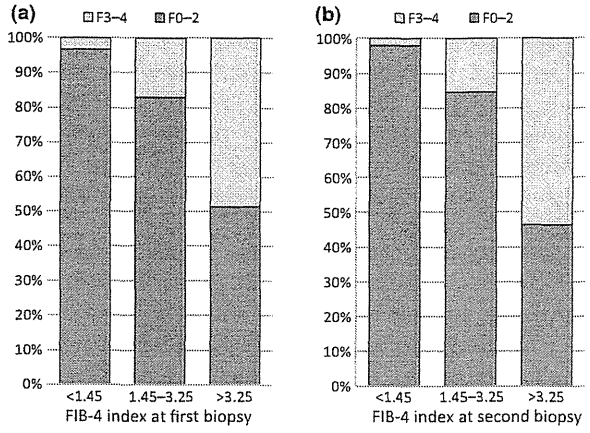

Fig. 1 Comparison of the FIB-4 index and liver fibrosis stage. Patients were categorized into three groups according to the FIB-4 index using cut-off values of < 1.45, 1.45–3.25, > 3.25 at liver biopsy. The lower bar chart (dark grey) indicates patients with F0–2, while the upper bar chart (light grey) indicates patients with F3–4. (a) comparison of the FIB-4 index and liver fibrosis stage at first biopsy and (b) at second biopsy.

Predictive factors for the progression of fibrosis

Higher level of ΔAST/year, lower level of ΔALT/year, lower level of ΔPlatelet counts/year and higher level of the ΔFIB-4/year were significantly associated with the progression of fibrosis overtime (Table 3). Multivariate analysis demonstrated that only the ΔFIB-4 index/year was an independent predictive factor for the progression of fibrosis stage ($P = 0.03$) with an odds ratio of 3.70 (95% CI:1.07–12.5).

Correlation between the degree of changes in the fibrosis stage and the ΔFIB-4 index per year

When the patients were categorized into five groups according to the degree of changes in the fibrosis stage per year (< −0.2, −0.2 – < 0, 0, > 0 – 0.2 and > 0.2), median value of the ΔFIB-4 index/year was −0.29, −0.02, 0.04, 0.16 and 0.47, respectively. The FIB-4 index reduced along the regression of the fibrosis stage, while the FIB-4 index increased along the progression of the fibrosis stage, which showed a significant correlation ($P < 0.001$) (Fig. 2).

Prediction of progression to cirrhosis by the changes in the FIB-4 index per year

The area under the receiver operating characteristic curve of the ΔFIB-4 index/year for the prediction of advancement to cirrhosis was 0.910. By the ΔFIB-4 index/year of 0.4, the sensitivity and specificity for the prediction of advancement to cirrhosis was 80% and 91%. The cumulative incidence of fibrosis progression to cirrhosis, at 5 and 10 years, was 34% and 59%, respectively, in patients with the ΔFIB-4 index/year ≥0.4, whereas it was 0% and 3% in those with the ΔFIB-4 index/year <0.4 ($P < 0.001$) (Fig. 3).

DISCUSSION

Recently, noninvasive markers of liver fibrosis have been used as a predictive factor of liver-related outcome such as

Table 3 Factors associated with the progression of liver fibrosis

	Progression of Liver fibrosis	Nonprogression of Liver fibrosis	*P*-value
Gender (male/female)	31/42	118/123	0.33
Age at first biopsy (years)	54.4 ± 8.7	53.5 ± 10.2	0.50
AST at first biopsy (IU/L)	63.9 ± 35.0	64.8 ± 37.3	0.85
ALT at first biopsy (IU/L)	86.5 ± 58.4	88.1 ± 59.2	0.84
Platelet counts at first biopsy (10^9/L)	15.8 ± 4.6	16.7 ± 4.8	0.16
Change between biopsies			
ΔAST (IU/L)/year	3.8 ± 19.5	−4.1 ± 14.8	<0.001
ΔALT (IU/L)/year	−1.9 ± 28.4	7.2 ± 22.6	0.005
ΔPlatelet counts (10^9/L)/year	−4.1 ± 9.5	−0.002 ± 9.5	0.001
ΔFIB-4 index/year	0.31 ± 0.52	−0.005 ± 0.37	<0.001

ΔAST/year: (AST at the second liver biopsy – AST at the first liver biopsy) /interval between paired biopsies (years); ΔALT/year: (ALT at the second liver biopsy – ALT at the first liver biopsy) /interval between paired biopsies (years); ΔPlatelet counts/year: (platelet counts at the second liver biopsy –platelet counts at the first liver biopsy) /interval between paired biopsies (years); ΔFIB-4 index /year: (the FIB-4 index at the second liver biopsy – the FIB-4 index at the first liver biopsy) /interval between paired biopsies (years).

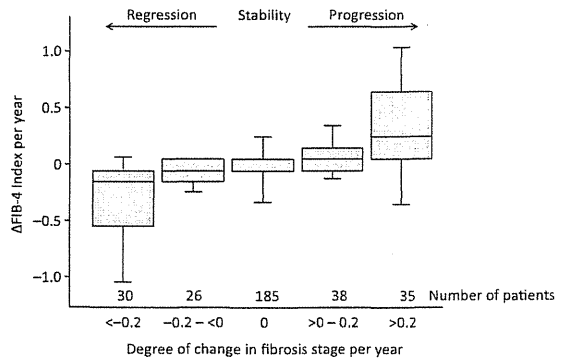

Fig. 2 Correlation between the degree of changes in the fibrosis stage and the ΔFIB-4 index per year. Boxplot of the ΔFIB-4 index/year is shown according to the degree of changes in the fibrosis stage per year. The bottom and top of each box represent the 25 and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and the error bar indicates the 5 and 95th percentiles.

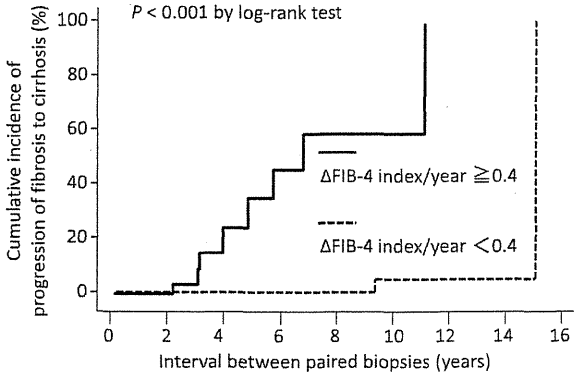

Fig. 3 Cumulative incidence of fibrosis progression to cirrhosis. Patients were categorized into two groups according to the ΔFIB-4 index/year using cut-off value of < 0.4 or ≥ 0.4.

mortality [22–24] or HCC development [24–26] in patients with chronic liver disease. There have been few studies that investigated the association between changes of noninvasive markers and liver-related outcome [27–29]. However, it is still unclear whether there is a relation between the time-course changes in the value of noninvasive markers and progression of liver fibrosis.

The aim of the study was to evaluate the utility of the real-time assessment of the FIB-4 index for the prediction of time-course progression in liver fibrosis. We have shown that the FIB-4 index reduced along the regression of the fibrosis stage, while the FIB-4 index increased along the progression of the fibrosis stage. These results indicate that the measurement of the time-course changes in the FIB-4 index may be useful for the noninvasive and real-time estimation of the progression in liver fibrosis overtime.

Although the gold standard for diagnosis of liver fibrosis is liver biopsy, there are a variety of problems including invasiveness and sampling errors [6]. Diagnostic methods of liver fibrosis by measurement of elasticity of the liver by ultrasonography [10–14] have been developed, but these modalities are not widely available.

The FIB-4 index has an advantage among these noninvasive liver fibrosis diagnostic methods. Firstly, it is quite easily calculated. The parameters required for calculation are only age, AST, ALT and platelet counts, which are measured at the routine examination of patients with liver disease. Therefore, additional blood collection is unnecessary, and the index can be calculated at no cost. Secondly, because of its simple calculation, it is possible to evaluate the clinical conditions in a real-time manner. Repeated measurements of the FIB-4 index make it possible to predict deterioration in liver fibrosis continuously over time. Because no special equipment or system is necessary, and objective data on the clinical conditions are provided in a real-time manner, the FIB-4 index is simple and convenient compared with other noninvasive liver fibrosis diagnostic methods.

It is widely known that a decrease in platelet counts is useful for the prediction of the progression of fibrosis stage [30]. We have reported that elevated AST or ALT is also associated with the progression of liver fibrosis [31]. However, the results of this study showed that a change in the FIB-4 index over time was a more useful factor for the prediction of the progression of fibrosis stage than AST, ALT and changes in platelet counts.

Liver biopsy is still an important examination as the gold standard for diagnosis of liver fibrosis, but time-course changes cannot be readily observed by repeated biopsies because of its invasiveness. On the other hand, it is possible to estimate the progression of liver fibrosis by repeated measurement of the FIB-4 index. Therefore, two examinations should be combined: liver biopsy may be utilized to determine the baseline of fibrosis stage, and the serial measurement of the FIB-4 index may be utilized to predict changes of fibrosis stages overtime in a real-time manner.

In conclusion, we believe that measurement of the time-course changes in the FIB-4 index is useful for the noninvasive and real-time estimation of the progression in liver fibrosis.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

No conflicts of interest exist for all authors.

REFERENCES

1 Dienstag JL. The role of liver biopsy in chronic hepatitis C. *Hepatology* 2002; 5(Suppl 1): S152–S160.
2 Benvegnu L, Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut* 2004; 53(5): 744–749.
3 Serfaty L, Aumaitre H, Chazouilleres O *et al.* Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998; 27(5): 1435–1440.
4 Gebo KA, Herlong HF, Torbenson MS *et al.* Role of liver biopsy in management of chronic hepatitis C: a systematic review. *Hepatology* 2002; 5(Suppl 1): S161–S172.
5 Saadeh S, Cammell G, Carey WD, Younossi Z, Barnes D, Easley K. The role of liver biopsy in chronic hepatitis C. *Hepatology* 2001; 33(1): 196–200.
6 Bravo AA, Sheth SG, Chopra S. Liver biopsy. *N Engl J Med* 2001; 344(7): 495–500.
7 Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003; 38(6): 1449–1457.
8 Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. *J Hepatol* 2003; 39(2): 239–244.
9 The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. *Hepatology* 1994; 20(1 Pt 1): 15–20.
10 Sandrin L, Fourquet B, Hasquenoph JM *et al.* Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003; 29(12): 1705–1713.
11 Ganne-Carrie N, Ziol M, de Ledinghen V *et al.* Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. *Hepatology* 2006; 44(6): 1511–1517.
12 Foucher J, Chanteloup E, Vergniol J *et al.* Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006; 55(3): 403–408.
13 Castera L, Vergniol J, Foucher J *et al.* Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; 128(2): 343–350.
14 Tatsumi C, Kudo M, Ueshima K *et al.* Noninvasive evaluation of hepatic fibrosis using serum fibrotic markers, transient elastography (FibroScan) and real-time tissue elastography. *Intervirology* 2008; 51(Suppl 1): 27–33.
15 Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. *Gastroenterology* 1988; 95(3): 734–739.
16 Wai CT, Greenson JK, Fontana RJ *et al.* A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; 38(2): 518–526.
17 Lin ZH, Xin YN, Dong QJ *et al.* Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology* 2011; 53(3): 726–736.
18 Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001; 357(9262): 1069–1075.
19 Sebastiani G, Vario A, Guido M *et al.* Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. *J Hepatol* 2006; 44(4): 686–693.
20 Sterling RK, Lissen E, Clumeck N *et al.* Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006; 43(6): 1317–1325.
21 Vallet-Pichard A, Mallet V, Nalpas B *et al.* FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. *Hepatology* 2007; 46(1): 32–36.
22 Vergniol J, Foucher J, Terrebonne E *et al.* Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. *Gastroenterology* 2011; 140(7): 1970–1979. 1979 e1971-1973.
23 Nunes D, Fleming C, Offner G *et al.* Noninvasive markers of liver fibrosis are highly predictive of liver-related death in a cohort of HCV-infected individuals with and without HIV infection. *Am J Gastroenterol* 2010; 105(6): 1346–1353.
24 Fung J, Lai CL, Seto WK, Wong DK, Yuen MF. Prognostic significance of liver stiffness for hepatocellular carcinoma and mortality in HBeAg-negative chronic hepatitis B. *J Viral Hepat* 2011; 18(10): 738–744.
25 Masuzaki R, Tateishi R, Yoshida H *et al.* Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. *Hepatology* 2009; 49(6): 1954–1961.
26 Jung KS, Kim SU, Ahn SH *et al.* Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). *Hepatology* 2011; 53(3): 885–894.
27 Vergniol J, Foucher J, Castera L *et al.* Changes of non-invasive markers and FibroScan values during HCV treatment. *J Viral Hepat* 2009; 16(2): 132–140.
28 Mummadi RR, Petersen JR, Xiao SY, Snyder N. Role of simple biomarkers in predicting fibrosis progression in HCV infection. *World J Gastroenterol* 2010; 16(45): 5710–5715.
29 Jain MK, Seremba E, Bhore R *et al.* Change in fibrosis score as a predictor of mortality among HIV-infected patients with viral hepatitis. *AIDS Patient Care STDS* 2012; 26(2): 73–80.
30 Poynard T, Bedossa P. Age and platelet count: a simple index for predicting the presence of histological lesions in patients with antibodies to hepatitis C virus. METAVIR and CLINIVIR Cooperative Study Groups. *J Viral Hepat* 1997; 4(3): 199–208.
31 Kurosaki M, Matsunaga K, Hirayama I *et al.* The presence of steatosis and elevation of alanine aminotransferase levels are associated with fibrosis progression in chronic hepatitis C with non-response to interferon therapy. *J Hepatol* 2008; 48(5): 736–742.

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Original Article

Prospective comparison of real-time tissue elastography and serum fibrosis markers for the estimation of liver fibrosis in chronic hepatitis C patients

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Aim: Real-time tissue elastography (RTE) is a non-invasive method for the measurement of tissue elasticity using ultrasonography. Liver fibrosis (LF) index is a quantitative method for evaluation of liver fibrosis calculated by RTE image features. This study aimed to investigate the significance of LF index for predicting liver fibrosis in chronic hepatitis C patients.

Methods: In this prospective study, 115 patients with chronic hepatitis C who underwent liver biopsy were included, and the diagnostic accuracy of LF index and serum fibrosis markers was evaluated.

Results: RTE imaging was successfully performed on all patients. Median LF index in patients with F0–1, F2, F3 and F4 were 2.61, 3.07, 3.54 and 4.25, respectively, demonstrating a stepwise increase with liver fibrosis progression ($P < 0.001$). LF index (odds ratio [OR] = 5.3, 95% confidence interval [CI] = 2.2–13.0) and platelet count (OR = 0.78, 95% CI = 0.68–0.89) were independently associated with the presence of advanced fibrosis (F3–4). Further, LF index was independently associated with the presence of minimal fibrosis (F0–1) (OR = 0.25, 95% CI = 0.11–0.55). The area under the receiver-operator curve (AUROC) of LF index for predicting advanced fibrosis (0.84) was superior to platelets (0.82), FIB-4 index (0.80) and aspartate aminotransferase/platelet ratio index (APRI) (0.76). AUROC of LF index (0.81) was superior to platelets (0.73), FIB-4 index (0.79) and APRI (0.78) in predicting minimal fibrosis.

Conclusion: LF index calculated by RTE is useful for predicting liver fibrosis, and diagnostic accuracy of LF index is superior to serum fibrosis markers.

Key words: chronic hepatitis C, fibrosis, liver fibrosis index, real-time tissue elastography

INTRODUCTION

AN ADVANCED STAGE of liver fibrosis in chronic hepatitis C (CHC) is associated with hepatocellular carcinoma development and complications such as esophageal variceal bleeding and liver failure.[1,2] Therefore, accurate evaluation of the stage of liver fibrosis is most important in clinical practice. Liver biopsy is considered to be the golden standard for diagnosis of liver fibrosis.[3–5] However, this method may be inaccurate because of sampling errors and interobserver variations.[6,7]

Improvements in a variety of non-invasive methods for evaluating liver fibrosis have recently emerged as alternatives to liver biopsy. Liver fibrosis was reportedly predicted by measurement of liver stiffness using transient elastography[8,9] and acoustic radiation force impulse (ARFI).[10,11] As assessed by blood laboratory tests, the aspartate aminotransferase (AST)/alanine

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aminotransferase (ALT) ratio,[12] AST/platelet ratio index (APRI),[13,14] and FIB-4 index[15,16] have been reported to be useful for the prediction of liver fibrosis. We previously reported that the FIB-4 index is useful for the prediction of liver fibrosis progression.[17]

Real-time tissue elastography (RTE) is a non-invasive method for the measurement of tissue elasticity using ultrasonography.[18] RTE calculates the relative hardness of tissue from the degree of tissue distortion and displays this information as a color image. RTE was recently reported to be useful for predicting liver fibrosis.[19,20] To increase the objectivity of the evaluation, an image analysis method to evaluate the strain image features and a new algorithm to deliver an index were proposed. Liver fibrosis (LF) index is a quantitative method for evaluation of liver fibrosis that is calculated by nine RTE image features, and the significance of LF index for predicting liver fibrosis has been reported.[21,22]

In the present study, we prospectively investigated the significance of LF index calculated by RTE for the prediction of liver fibrosis in CHC patients. Further, diagnostic accuracy for liver fibrosis was compared between LF index and serum fibrosis markers.

METHODS

Patients

A TOTAL OF 127 consecutive patients with CHC were prospectively investigated. All patients underwent liver biopsy at Musashino Red Cross Hospital between February 2011 and November 2012. Exclusion criteria comprised the following: (i) co-infection with hepatitis B virus ($n = 1$); (ii) co-infection with HIV ($n = 1$); (iii) history of autoimmune hepatitis or primary biliary cirrhosis ($n = 3$); (iv) alcohol abuse (intake of alcohol equivalent to pure alcohol ≥40 g/day) ($n = 0$); (v) portal tracts of biopsy sample of less than five ($n = 7$); and (vi) presence of serious heart disease ($n = 0$). After exclusion, 115 patients were enrolled in this study. Written informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional ethics review committees (application no. 24007).

Histological evaluation

Liver biopsy specimens were laparoscopically obtained using 13-G needles ($n = 93$). When laparoscopy was not conducted due to a history of upper abdominal surgery, percutaneous ultrasound-guided liver biopsy was performed using 15-G needles ($n = 22$). Specimens were fixed, paraffin-embedded, and stained with hematoxylin–eosin and Masson-trichrome. A biopsy sample with minimum portal tracts of five was required for diagnosis. All liver biopsy samples were independently evaluated by two senior pathologists who were blinded to the clinical data. Fibrosis staging was categorized according to the METAVIR score:[23] F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Activity of necroinflammation was graded on a scale of 0–3: A0, no activity; A1, mild activity; A2, moderate activity; and A3, severe activity. Percentage of steatosis was quantified by determining the average proportion of hepatocytes affected by steatosis and graded on a scale of 0–3: grade 0, no steatosis; grade 1, 1–33%; grade 2, 34–66%; and grade 3, 67% and over.

Clinical and biological data

The age and sex of the patients were recorded. Serum samples were collected within 1 day prior to liver biopsy and the following variables were obtained through serum sample analysis: AST, ALT and platelet count. FIB-4 index and APRI were calculated according to the published formula appropriate to each measure.[13,15]

RTE and LF index

Real-time tissue elastography was performed using HI VISION Preirus (Hitachi Aloka Medical, Tokyo, Japan) and the EUP-L52 linear probe (3–7 MHz; Hitachi Aloka Medical) within 3 days of liver biopsy. RTE was performed on the right lobe of the liver through the intercostal space. An RTE image was induced by heartbeats. Five RTE images were collected for each patient and analyzed to calculate nine image features. RTE method and the equation that calculates LF index using nine image features has been previously detailed.[22] Results are expressed as mean LF index of all measurements. Two hepatologists (N. T. and K. Tsuchiya, with 8 and 16 years of experience, respectively) performed RTE. In 32 patients with CHC, LF index was measured independently by two examiners. The correlation coefficient of LF index between two examiners was 0.85 ($P \leq 0.001$).

Statistical analysis

Correlations between LF index and histological fibrosis stage were analyzed using Spearman's rank correlation coefficients. Categorical variables were compared using Fisher's exact test, and continuous variables were compared using Mann–Whitney *U*-test. $P < 0.05$ was considered statistically significant. Logistic regression was

used for multivariate analysis. Receiver–operator curves (ROC) were constructed, and the area under the ROC (AUROC) was calculated. Optimal cut-off values were selected, to maximize sensitivity, specificity and diagnostic accuracy. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated by using cut-offs obtained by ROC. SPSS software ver. 15.0 (SPSS, Chicago, IL, USA) was used for analyses.

RESULTS

Patient characteristics

THE CHARACTERISTICS OF all 115 patients are listed in Table 1. F0–1 was diagnosed in 52 cases (45%), F2 in 31 (27%), F3 in 20 (17%) and F4 in 12 (11%). Mean values of LF index of F0 (2.62) and F1 (2.60) were not significantly different ($P = 0.9$), and only six patients with F0 were included in this study. Therefore, patients with F0 and F1 were integrated for the analysis. RTE imaging was successfully performed in all patients, and LF index was calculated.

Relationship between histological findings and LF index by RTE

The median value of LF index compared with the METAVIR fibrosis stage is shown in Figure 1. Median LF index in patients with F0–1, F2, F3 and F4 were 2.61, 3.07, 3.54 and 4.25, respectively, demonstrating a stepwise increase with liver fibrosis progression ($P < 0.001$). LF index of each fibrosis stage significantly differed from each other (F0–1 vs F2, $P < 0.001$; F0–1 vs F3, $P < 0.001$; F0–1 vs F4, $P < 0.001$; F2 vs F3, $P = 0.009$; F2 vs F4, $P = 0.001$). On the other hand, mean values of LF index in patients with steatosis grade 0, 1 and 2 were 2.99, 3.29 and 2.60, respectively, demonstrating no significant correlation (Fig. 2a). LF index was compared with steatosis grade for each fibrosis stage. LF index was not significantly different between patients with steatosis and without steatosis (Fig. 2b).

Liver fibrosis index was compared with histological activity. A significant correlation existed between histological activity and fibrosis stage. Therefore, the relationship between LF index and histological activity was examined by each fibrosis stage. In patients with F0–1, the mean LF index of A1, A2 and A3 was 2.60, 2.58 and 2.40, respectively, demonstrating no significant correlation. Similarly, in patients with F2, F3 and F4, there was no significant correlation between LF index and histological activity (Fig. 3).

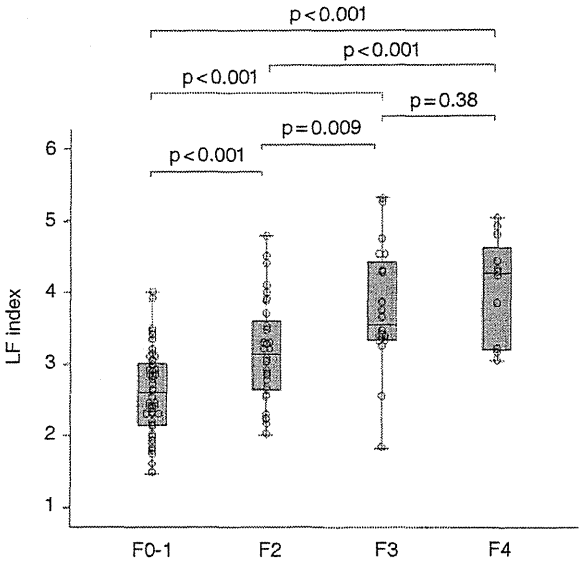

Figure 1 Correlation between liver fibrosis (LF) index calculated by real-time tissue elastography and fibrosis stage. Box plot of the LF index is shown according to each fibrosis stage. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values.

Table 1 Patient characteristics

Characteristics	Patients ($n = 115$)
Female/male	68/47
Age (years)	57.9 ± 10.9
AST (IU/L)	55.7 ± 44.9
ALT (IU/L)	63.2 ± 56.3
Platelet counts ($\times 10^9$/L)	162 ± 53
Portal tracts of biopsy samples	12.6 ± 5.0
Fibrosis stage	
F0–1 (%)	51 (44)
F2 (%)	32 (28)
F3 (%)	20 (17)
F4 (%)	12 (11)
Histological activity	
A0 (%)	0 (0)
A1 (%)	75 (65)
A2 (%)	34 (30)
A3 (%)	6 (5)
Steatosis grade	
Grade 0 (%)	65 (57)
Grade 1 (%)	47 (41)
Grade 2 (%)	3 (2)
Grade 3 (%)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

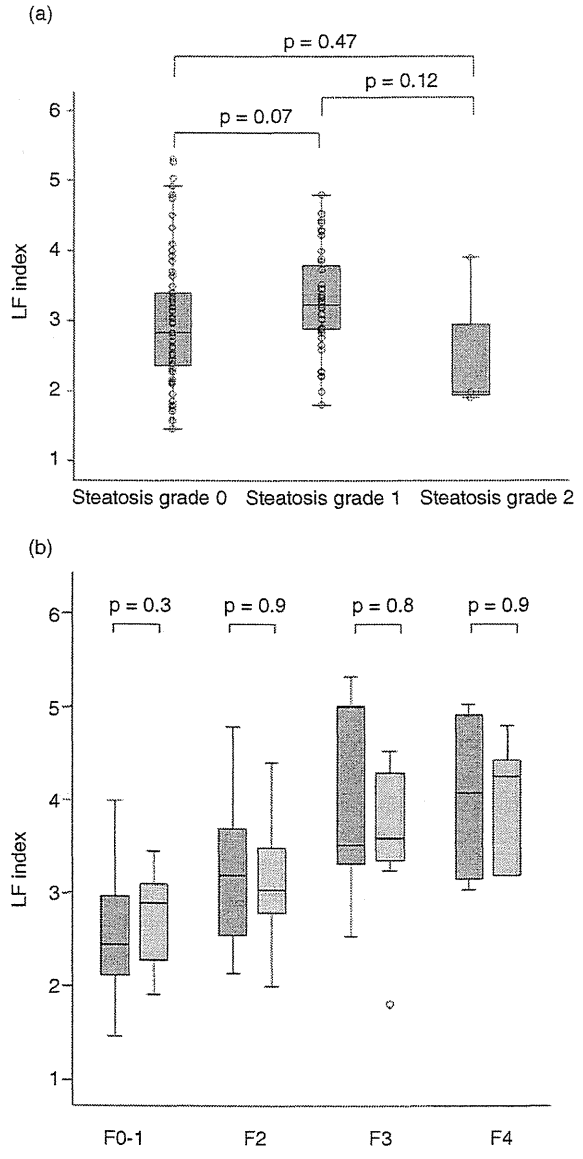

Figure 2 (a) Correlation between liver fibrosis (LF) index and steatosis grade. Box plot of the LF index is shown according to each steatosis grade. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values. (b) Box plot of LF index for each fibrosis stage in relation to degree of steatosis grade. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values. Dark grey bar chart indicates steatosis grade 0. Light grey bar chart indicates steatosis grade 1–2.

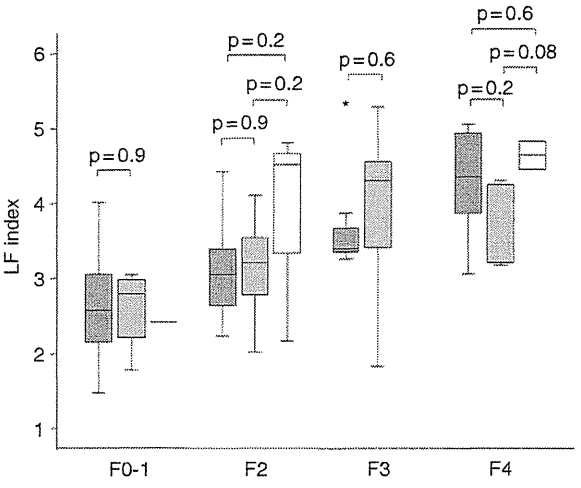

Figure 3 Box plot of liver fibrosis (LF) index for each fibrosis stage in relation to degree of necroinflammatory activity. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values. Dark grey bar chart indicates activity grade 1. Light grey bar chart indicates activity grade 2. White bar chart indicates activity grade 3.

Comparison of variables associated with the presence of advanced fibrosis (F3–4) by univariate and multivariate analysis

Variables associated with the presence of advanced fibrosis (F3–4) were assessed by univariate and multivariate analysis (Table 2). The variables of age ($P = 0.03$) and LF index ($P < 0.001$) were significantly higher, and the variable of platelets ($P < 0.001$) was significantly lower in patients with advanced fibrosis than in patients with F0–2. Multivariate analysis showed that LF index (odds ratio [OR] = 5.3, 95% confidence interval [CI] =2.2–13.0) and platelets (OR = 0.78, 95% CI = 0.68–0.89) were independently associated with the presence of advanced fibrosis.

Comparison of variables associated with the presence of minimal fibrosis (F0–1) by univariate and multivariate analysis

Variables associated with the presence of minimal fibrosis (F0–1) were assessed by univariate and multivariate analysis (Table 3). The variables of age ($P < 0.001$), AST ($P = 0.02$) and LF index ($P < 0.001$) were significantly lower, and the variable of platelets ($P < 0.001$) was significantly higher in F0–1 patients than F2–4 patients.

Table 2 Variables associated with the presence of advanced fibrosis (F3–4) by univariate and multivariate analysis

	F0–2 ($n = 83$)	F3–4 ($n = 32$)	*P*-value (Univariate)	Odds ratio (95% CI) (Multivariate)
Age (years)	56.6 ± 10.9	61.3 ± 10.4	0.03	
Sex (female/male)	51/32	17/15	0.41	
AST (IU/L)	52.3 ± 43.3	64.4 ± 48.3	0.19	
ALT (IU/L)	62.9 ± 60.6	63.9 ± 44.2	0.93	
Platelets ($\times 10^9$/L)	179 ± 47	117 ± 42	<0.001	0.78 (0.68–0.89)
LF index	2.81 ± 0.69	3.86 ± 0.81	<0.001	5.30 (2.16–13.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; LF, liver fibrosis.

Multivariate analysis showed that LF index was independently associated with the presence of minimal fibrosis (OR = 0.25, 95% CI = 0.11–0.55).

Diagnostic accuracy of RTE and serum fibrosis markers

Receiver–operator curves of LF index, platelets, FIB-4 index and APRI for predicting advanced fibrosis (F3–4), and minimal fibrosis (F0–1) were plotted, as shown in Figure 4. AUROC of LF index for predicting advanced fibrosis (0.84) was superior to platelets (0.82), FIB-4 index (0.80) and APRI (0.76). Similarly, for predicting minimal fibrosis, AUROC of LF index (0.81) was superior to platelets (0.73), FIB-4 index (0.79) and APRI (0.78). The corresponding sensitivities, specificities, PPV and NPV are detailed in Table 4.

DISCUSSION

IMPROVEMENTS IN VARIOUS methods for prediction of liver fibrosis have recently emerged as alternatives to liver biopsy. RTE is a non-invasive method for the measurement of tissue elasticity using ultrasonography. The utility of RTE for evaluating liver fibrosis is reported in a few studies.[18–22] However, for utilizing LF index, one of the equations used to calculate tissue elasticity by RTE is still unclear. The aim of this study was to investigate the significance of LF index for the prediction of liver fibrosis in CHC patients.

In this prospective study, we found that LF index is a useful predictive factor for diagnosis of the fibrosis stage in CHC patients. Increase in LF index significantly correlated with progression of the fibrosis stage and LF index was able to predict the presence of advanced fibrosis and minimal fibrosis. Previous studies reported the utility of LF index for prediction of the liver fibrosis stage.[21,22] In this study, LF index differed significantly between patients with F0–1 and F2; thus, LF index was especially useful for prediction of minimal fibrosis. This may be due to a sufficient number of patients with F0–1 and F2 included in the present study. This is an advantage of LF index because other quantitative methods by RTE could not discriminate patients with F0–1 and F2.[19,20] On the other hand, there is a possibility that a similar result may be obtained for differentiation of F3 and F4 if a large number of patients with advanced fibrosis was included.

Previous studies did not compare the diagnostic accuracy of LF index and serum fibrosis markers. We revealed that LF index performed better than serum fibrosis

Table 3 Variables associated with the presence of minimal fibrosis (F0–1) by univariate and multivariate analysis

	F0–1 ($n = 51$)	F2–4 ($n = 64$)	*P*-value (Univariate)	Odds ratio (95% CI) (Multivariate)
Age (years)	54.0 ± 11.9	61.0 ± 9.0	<0.001	
Sex (female/male)	31/20	37/27	0.74	
AST (IU/L)	44.5 ± 42.6	64.6 ± 44.9	0.02	
ALT (IU/L)	53.0 ± 56.3	71.3 ± 55.5	0.08	
Platelets ($\times 10^9$/L)	186 ± 47	142 ± 50	<0.001	
LF index	2.60 ± 0.59	3.51 ± 0.84	<0.001	0.25 (0.11–0.55)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; LF, liver fibrosis.

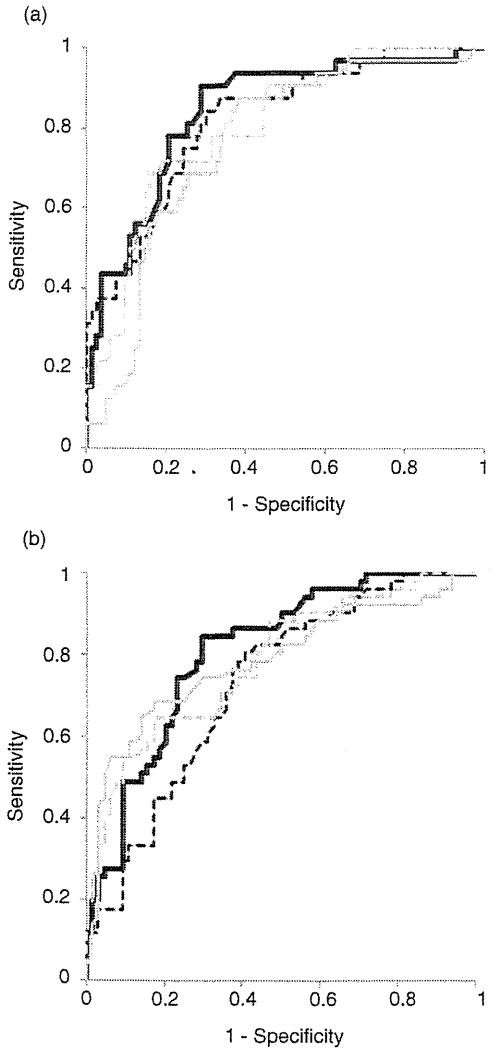

Figure 4 Receiver–operator curves (ROC) of liver fibrosis (LF) index and serum fibrosis markers. (a) ROC for diagnosis of significant fibrosis (F3–4). (b) ROC for diagnosis of minimal fibrosis (F0–1). —, LF index; ····, platelets; , aspartate aminotransferase-to-platelet ratio index; , FIB-4 index.

markers based on blood laboratory tests for predicting liver fibrosis.

Transient elastography has been most commonly used to measure liver stiffness and is established in clinical practice to evaluate liver fibrosis.[8,9] RTE exhibits some advantages compared with transient elastography. In this study, RTE imaging was successfully performed in all patients, and LF index was calculated. Although transient elastography has high diagnostic capabilities when it comes to liver fibrosis, measurements are sometimes impossible in patients with severe obesity and ascites.[24] Reproducibility of transient elastography was reportedly lower in patients with steatosis, inflammation, increased body mass index and lower degrees of liver fibrosis.[25–27] On the other hand, LF index is measured by ultrasound guidance that facilitates the identification of a suitable location for elastographic measurement, thereby resulting in a higher number of patients with valid results.

Unlike transient elastography, another advantage of LF index is that the results are not influenced by the presence of inflammation and steatosis. It was reported that LF index is not useful in patients with steatosis.[22] However, LF index was not significantly different between patients with and without steatosis in the present study even after stratification by fibrosis stage. Thus, LF index was useful for prediction of fibrosis in CHC patients regardless of steatosis. Because LF index of each activity grade and steatosis grade did not differ from each other, estimation of liver fibrosis by LF index demonstrated higher reproducibility than transient elastography.

In previously reports, diagnostic accuracy of liver fibrosis using RTE was inferior to transient elastography;[28] however, other studies have reported contrasting results.[19] The reason for this variability is probably because RTE technology and the equations used to calculate tissue elasticity are rapidly changing. The utility of elastic ratio, another RTE method for evaluation of liver fibrosis, was reported.[20] The elastic ratio is the ratio between the tissue compressibility of the liver and that of the intrahepatic small vessel. The AUROC of elastic ratio for predicting advanced fibrosis was 0.94 and was superior to LF index. Further, ARFI and real-time shear wave elastography were reported to have a high diagnostic accuracy of liver fibrosis.[10,11,29] There are currently no studies that directly compare LF index and those methods for diagnostic value of liver fibrosis. Therefore, further studies are needed to fully explore the potential of RTE, especially with regard to LF index.

Our study had several limitations. The number of patients with advanced fibrosis was small. The potential of LF index to differentiate patients with F3 and F4 needs to be explored with a large number of patients. Further, validation study is needed to evaluate the diagnostic accuracy of fibrosis stage, especially in comparison with other modalities.

In conclusion, LF index calculated by RTE is useful for predicting liver fibrosis, and diagnostic accuracy of LF index is superior to that of serum fibrosis markers.

Table 4 Diagnostic performance of LF index and serum fibrosis markers

	F0–2 vs F3–4					F0–1 vs F2–4				
	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
LF index	0.84	90.6	71.1	54.7	95.2	0.81	84.3	70.3	69.4	84.9
Platelets	0.82	87.5	66.3	50.0	93.2	0.73	80.4	59.4	61.2	79.2
FIB-4 index	0.80	71.9	81.9	60.5	88.3	0.79	54.9	90.6	82.3	71.6
APRI	0.76	87.5	61.4	46.7	92.7	0.78	64.7	85.9	78.6	75.3

APRI, aspartate aminotransferase/platelet ratio index; AUROC, area under the receiver–operator curve; NPV, negative predictive value; PPV, positive predictive value.

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REFERENCES

1 Serfaty L, Aumaitre H, Chazouilleres O *et al.* Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998; 27: 1435–40.
2 Benvegnu L, Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut* 2004; 53: 744–9.
3 Dienstag JL. The role of liver biopsy in chronic hepatitis C. *Hepatology* 2002; 36: S152–60.
4 Gebo KA, Herlong HF, Torbenson MS *et al.* Role of liver biopsy in management of chronic hepatitis C: a systematic review. *Hepatology* 2002; 36: S161–72.
5 Namiki I, Nishiguchi S, Hino K *et al.* Management of hepatitis C; Report of the Consensus Meeting at the 45th Annual Meeting of the Japan Society of Hepatology (2009). *Hepatol Res* 2010; 40: 347–68.
6 Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003; 38: 1449–57.
7 Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology* 1994; 20: 15–20.
8 Sandrin L, Fourquet B, Hasquenoph JM *et al.* Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003; 29: 1705–13.
9 Friedrich-Rust M, Ong MF, Martens S *et al.* Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. *Gastroenterology* 2008; 134: 960–74.
10 Friedrich-Rust M, Wunder K, Kriener S *et al.* Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. *Radiology* 2009; 252: 595–604.
11 Palmeri ML, Wang MH, Rouze NC *et al.* Noninvasive evaluation of hepatic fibrosis using acoustic radiation force-based shear stiffness in patients with nonalcoholic fatty liver disease. *J Hepatol* 2011; 55: 666–72.
12 Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. *Gastroenterology* 1988; 95: 734–9.
13 Wai CT, Greenson JK, Fontana RJ *et al.* A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; 38: 518–26.
14 Lin ZH, Xin YN, Dong QJ *et al.* Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology* 2011; 53: 726–36.
15 Sterling RK, Lissen E, Clumeck N *et al.* Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006; 43: 1317–25.
16 Vallet-Pichard A, Mallet V, Nalpas B *et al.* FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology* 2007; 46: 32–6.
17 Tamaki N, Kurosaki M, Tanaka K *et al.* Noninvasive estimation of fibrosis progression overtime using the FIB-4 index in chronic hepatitis C. *J Viral Hepat* 2013; 20: 72–6.
18 Friedrich-Rust M, Ong MF, Herrmann E *et al.* Real-time elastography for noninvasive assessment of liver fibrosis in chronic viral hepatitis. *AJR Am J Roentgenol* 2007; 188: 758–64.
19 Morikawa H, Fukuda K, Kobayashi S *et al.* Real-time tissue elastography as a tool for the noninvasive assessment of liver stiffness in patients with chronic hepatitis C. *J Gastroenterol* 2011; 46: 350–8.
20 Koizumi Y, Hirooka M, Kisaka Y *et al.* Liver fibrosis in patients with chronic hepatitis C: noninvasive diagnosis by means of real-time tissue elastography – establishment of the method for measurement. *Radiology* 2011; 258: 610–17.

21 Tatsumi C, Kudo M, Ueshima K *et al.* Non-invasive evaluation of hepatic fibrosis for type C chronic hepatitis. *Intervirology* 2010; **53**: 76–81.
22 Tomeno W, Yoneda M, Imajo K *et al.* Evaluation of the Liver Fibrosis Index calculated by using real-time tissue elastography for the non-invasive assessment of liver fibrosis in chronic liver diseases. *Hepatol Res* 2012; **12**: 12023.
23 Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996; **24**: 289–93.
24 Castera L, Foucher J, Bernard PH *et al.* Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology* 2010; **51**: 828–35.
25 Fraquelli M, Rigamonti C, Casazza G *et al.* Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. *Gut* 2007; **56**: 968–73.
26 Arena U, Vizzutti F, Abraldes JG *et al.* Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. *Gut* 2008; **57**: 1288–93.
27 Rizzo L, Calvaruso V, Cacopardo B *et al.* Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. *Am J Gastroenterol* 2011; **106**: 2112–20.
28 Colombo S, Buonocore M, Del Poggio A *et al.* Head-to-head comparison of transient elastography (TE), real-time tissue elastography (RTE), and acoustic radiation force impulse (ARFI) imaging in the diagnosis of liver fibrosis. *J Gastroenterol* 2012; **47**: 461–9.
29 Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. *Hepatology* 2012; **56**: 2125–33.

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Special Report

JSH Guidelines for the Management of Hepatitis C Virus Infection: A 2014 Update for Genotype 1

Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology*,**

1. INTRODUCTION

RECENTLY, THE MANAGEMENT of chronic hepatitis C virus (HCV) has been greatly advanced with introduction of direct-acting antiviral agents (DAAs) in clinical setting. In Japan, the first DAA, telaprevir (TVR), was approved for patients with chronic hepatitis C in 2011. Along with this, the Japan Society of Hepatology (JSH) produced the first clinical practice guideline for the management of HCV infection, "Guidelines for the Management of Hepatitis C Virus Infection" in May 2012 (English version, 2013[1]). It is our great pleasure that these Guidelines were welcomed and utilized by physicians and other health care providers in daily clinical practices in Japan.

Meanwhile, in September 2013, a second-generation DAA, simeprevir (SMV), was approved for use in Japan. According to Phase III trials in Japan and overseas, SMV has a robust therapeutic effect with better safety profiles compared to TVR. As a result, we have decided to update the clinical guidelines for HCV with launch of this new DAA. SMV has now been approved for use in patients with chronic hepatitis C with genotype 1 and high viral load, and therefore these current Guidelines are updated for patients in this group.

As stated in the previous Guidelines, this is a field that changes rapidly with the accumulation of new evidence, and evidence levels are not shown in the recommendations. At present, several other therapeutic agents are expected to be approved for daily use and we plan to revise these guidelines at appropriate intervals, as new evidence comes to hand.

2. SIMEPREVIR (SMV)

INHIBITORS OF HEPATITIS C virus (HCV) NS3-4A protease are classified into 2 groups on the basis of their molecular structures, linear inhibitors with no branches and macrocyclic inhibitors containing macrocycles. Macrocyclic small molecule compounds show superior affinity and selectivity for therapeutic target proteins.[2] Whereas TVR is a first-generation protease inhibitor with linear structure, SMV is a second-generation protease inhibitor with macrocyclic structure discovered during the optimization process for early protease inhibitors.[3] In vitro resistance testing has yielded different drug resistance profiles, due to their different structures, with cross resistance to SMV seen in TVR resistant mutations at amino acids 155 and 156, whereas mutations at amino acids 36, 54 and 170 were sensitive to SMV, and mutations at amino acids 80 and

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168 resistant to SMV alone.[4] Pharmacokinetic studies have shown that once daily administration of SMV provides effective plasma levels 24 h post-dose.[5] SMV shows inhibitory activity against HCV genotypes 1, 2, 4, 5 and 6, with particularly strong anti-proliferative action against genotypes 1a and 1b. In September 2013, the use of SMV in clinical setting was approved in combination with Peg-IFN + RBV in patients with chronic hepatitis C with genotype 1 and a high viral load (≥5.0 log IU/mL).

2.1 Therapeutic results

Phase II trials of SMV + Peg-IFN + RBV combination therapy for genotype 1 chronic hepatitis C include the Japanese DRAGON study (treatment-naïve patients),[6] and the overseas PILLAR study (treatment-naïve patients)[7] and the ASPIRE trial (relapsers following previous treatment and non-responders to previous treatment).[8] Based on the results of these studies, the SMV dosage was set at 100 mg once daily for clinical phase III studies in Japan, and 150 mg once daily for overseas studies. Published Japanese clinical phase III studies comprise the CONCERTO-1 (treatment-naïve patients),[9] CONCERTO-2 (non-responders to previous treatment),[10] CONCERTO-3 (relapsers following previous treatment),[10] and CONCERTO-4 (treatment-naïve patients, non-responders, and relapsers) trials.[11] Published overseas clinical phase III studies comprise the QUEST-1 (treatment-naïve patients),[12] QUEST-2 (treatment-naïve patients),[13] and PROMISE (relapsers) studies.[14] The subjects for the Japanese clinical trials were patients with chronic hepatitis C (excluding cirrhosis) with genotype 1 and a high viral load (≥5.0 log IU/mL), aged 20–70 years (Table 1).

2.1.1 Treatment-naïve patients

The protocol for the Japanese CONCERTO-1 trial,[9] conducted with IFN-naïve subjects, administered SMV 100 mg once daily + Peg-IFNα-2a + RBV triple therapy for the first 12 weeks, then Peg-IFNα-2a + RBV dual therapy for 12 or 36 weeks according to the response-guided therapy (RGT). Using this RGT, subjects with HCV RNA < 1.2 log IU/mL or undetectable after 4 weeks' treatment, and undetectable after 12 weeks, were administered Peg-IFNα-2a + RBV for 12 weeks (total treatment duration 24 weeks), and all other subjects for 36 weeks (total treatment duration 48 weeks). As a result, 99% of subjects met the response-guided criteria, and underwent 24 weeks of treatment. The SVR24 rate was 89% (109/123) for the triple therapy group, significantly higher than that of 57% (34/60) in the control group (Fig. 1).

Peg-IFNα-2b was used in the CONCERTO-4 trial,[11] conducted with IFN-naïve subjects, the same response-

Table 1A Characteristics of patients enrolled in CONCERTO-1/2/3

	Treatment-naïve		*Non-responders*		*Relapsers*
	SMV 12W	PBO	SMV 12W	SMV 24W	SMV 12W
	(n = 123)	(n = 60)	(n = 53)	(n = 53)	(n = 49)
male, %	31.7	40.0	50.9	49.1	40.8
age *	56 (23–69)	54.5 (30–69)	60 (30–70)	60 (24–70)	61 (22–70)
≥65, %	17.9	16.7	26.4	22.6	24.5
BMI, kg/m² *	22.0 (16.9–32.9)	22.5 (17.3–33.2)	22.3 (16.8–29.5)	21.9 (19.2–33.4)	22.3 (17.9–32.2)
IL28B SNP (rs8099917), %					
TT	61.7	70	15.1	11.3	71.4
TG	31.7	28.3	83	86.8	28.6
GG	1.6	1.7	1.9	1.9	0
HCV genotype 1b, %	98.4	98.3	100	94.3	98
HCV RNA at baseline, LogIU/mL *	6.3 (4.5–7.2)	6.4 (3.3–7.4)	6.4 (4.6–7.3)	6.4 (5.1–7.0)	6.5 (5.0–7.0)
previous IFN Tx					
IFN mono			7.5	3.8	4.1
IFN+RBV			7.5	7.5	8.2
Peg-IFN mono			0	1.9	4.1
Peg-IFN+RBV			84.9	86.8	83.7

* expressed as median (range).

Table 1B Characteristics of patients enrolled in CONCERTO-4

	Treatment-naïve	*Non-responders*	*Relapsers*
	SMV 12W	SMV 12W	SMV 12W, PR 48W
	(n = 24)	(n = 29)	(n = 26)
male, %	33.3	55.2	50
age *	60 (37–68)	60 (38–70)	53 (45–69)
≥65, %	20.8	31	15.4
BMI, kg/m^2 *	23.0 (18.1–30.2)	22.5 (18.1–31.9)	22.4 (16.9–34.3)
IL28B SNP (rs8099917), %			
TT	66.7	89.7	7.7
TG	33.3	10.3	80.8
GG	0	0	11.5
HCV genotype 1b, %	100	100	96.2
HCV RNA at baseline, LogIU/mL *	6.6 (5.4–7.0)	6.6 (4.9–7.4)	6.5 (5.1–7.4)
previous IFN Tx			
IFN mono		3.4	0
IFN+RBV		0	11.5
Peg-IFN mono		0	0
Peg-IFN+RBV		96.6	88.5

* expressed as median (range).

guided criteria were set, all subjects met the criteria and underwent 24 weeks of treatment, yielding an SVR24 rate of 92% (22/24) (Fig. 2).

In the overseas QUEST-1 study,[12] subjects were administered SMV 150 mg once daily + Peg-IFNα-2a + RBV triple therapy for the first 12 weeks, then response-guided criteria were set as for the CONCERTO-1 trial, with 85% of subjects meeting the criteria and undergoing 24 weeks of treatment. The overall SVR12 rate was 80%; 71% (105/147) in genotype 1a and 90% (105/117) in genotype 1b. The QUEST-2 study[13] set two groups, with either Peg-IFNα-2a or Peg-IFNα-2b, otherwise following the same

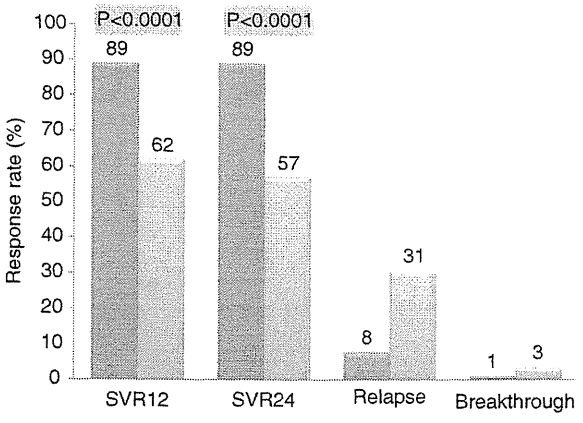

Figure 1 Therapeutic results for SMV + Peg-IFNα-2a + RBV triple therapy for treatment-naïve patients (from CONCERTO-1 trial[9]). ■, SMV + Peg-IFNα-2a + RBV; ■, Peg-IFNα-2a + RBV.

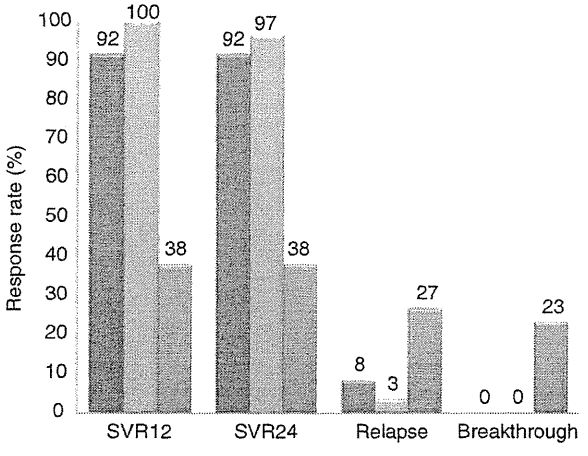

Figure 2 Therapeutic results for SMV + Peg-IFNα-2b + RBV triple therapy for treatment-naïve patients, non-responders, and relapsers (from CONCERTO-4 trial[11]). ■, treatment-naïve cases; ■, relapsers; ■, non-responders. Total treatment duration was 24W for treatment-naive and relapsers, and 48W for non-responders.

protocol as the QUEST-1 study for treatment durations. As a result, 91% of subjects met the criteria and underwent 24 weeks of treatment. The overall SVR12 rate was 81%; 80% (86/107) and 82% (123/150) in genotype 1a and 1b, respectively. The SVR12 rate for Peg-IFNα-2a and Peg-IFNα-2b was 88% and 78%, respectively. In both these studies, triple therapy including SMV yielded significantly higher SVR rates than for 48 weeks of Peg-IFN + RBV dual therapy.

In this way, clinical trials of SMV-based triple therapy regimens were conducted using a response-guided protocol that set a treatment duration of 24 or 48 weeks, with almost all subjects meeting the criteria for the shorter duration. The SVR rate for IFN-naïve subjects in the Japanese studies was 89–92%, and in the overseas studies it was 82–90% for genotype 1b, significantly higher than the SVR rate in the control groups administered 48 weeks of Peg-IFN + RBV dual therapy.

2.1.2 Relapsers following previous treatment

The Japanese CONCERTO-3 trial,[10] conducted with subjects who relapsed following previous IFN therapy, was conducted using a similar protocol to the CONCERTO-1 trial.[9] All subjects met the response-guided criteria and underwent 24 weeks of treatment, yielding an SVR24 rate of 90% (44/49) (Fig. 3). Similarly, the CONCERTO-4 trial,[11] conducted with relapsers, followed a similar therapeutic protocol to the CONCERTO-3 trial,[10] using Peg-IFNα-2b. All subjects met the response-guided criteria and underwent 24 weeks of treatment, yielding an SVR24 rate of 97% (28/29) (Fig. 2).

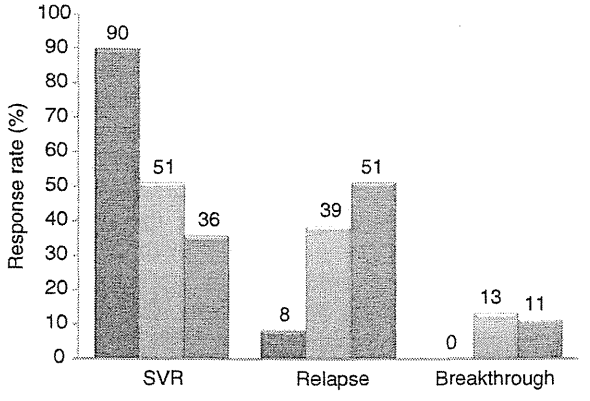

Figure 3 Therapeutic results for SMV + Peg-IFNα-2a + RBV triple therapy for non-responders and relapsers (from CONCERTO-2 and CONCERTO-3 trials[10]). ■, relapsers; ■, non-responders (SMV for 12 wks); ■, non-responders (SMV for 24 wks).

The overseas PROMISE study,[14] conducted with relapsers, was performed using a similar protocol to the QUEST-1 study. As a result, 93% of subjects met the response-guided criteria and underwent 24 weeks of treatment. The overall SVR12 rate was 79%; 70% (78/111) in genotype 1a and 86% (128/149) in genotype 1b.

In this way, in clinical trials of SMV-based triple therapy regimens with relapsers following previous IFN therapy, majority of subjects met the response-guided criteria and underwent 24 weeks of treatment. The SVR rate for the Japanese studies was 90–97%, and in the overseas studies it was 86% for genotype 1b, significantly higher than the SVR rate in the control groups administered 48 weeks of Peg-IFN + RBV dual therapy.

2.1.3 Non-responders to previous treatment

In the Japanese CONCERTO-2 trial,[10] non-responders to previous IFN therapy were administered SMV + Peg-IFNα-2a + RBV triple therapy for 12 weeks (SMV 12W group) or 24 weeks (SMV 24W group). The total treatment duration for both groups was set using response-guided criteria similar to those for the CONCERTO-1 trial,[9] with 96% and 98% of subjects, who completed 24 weeks of treatment respectively, meeting the criteria and finishing the treatment at 24 weeks. The SVR24 rate was 51% (27/53) for the SMV 12W group, and 36% (19/53) for the SMV 24W group (Fig. 3). In the CONCERTO-4 trial,[11] non-responders were administered SMV + Peg-IFNα-2b + RBV triple therapy for 12 weeks, followed by Peg-IFNα-2b + RBV dual therapy for 36 weeks, for a total treatment duration of 48 weeks. The SVR24 rate was 38% (10/26) (Fig. 2).

Although the Japanese CONCERTO-2[10] and CONCERTO-4[11] trials were conducted with non-responders, they did not conduct any further analyses subdividing non-responders into partial responders, with a decrease in the HCV RNA level by ≥2 log IU/mL at week 12 of the previous treatment, and null responders, with a decrease < 2 log IU/mL. On the other hand, the overseas phase II ASPIRE trial,[8] conducted with relapsers and non-responders, reported therapeutic results separately for partial responders and null responders. This trial assigned subjects to one of 3 groups, all with a total treatment period of 48 weeks. They were administered SMV + Peg-IFNα-2a + RBV triple therapy for 12 weeks or 24 weeks, followed by Peg-IFNα-2a + RBV dual therapy for the remaining time, or triple therapy for the entire 48 weeks. SMV was administered in a daily dosage of either 100 mg or 150 mg. The SVR rate for the SMV 12, 24 and 48 week

Table 2 Drugs contraindicated for co-administration with SMV (reproduced from[16])

Generic name	Trade name
Efavirenz	Stocrin
Rifampicin	Rifadin
Rifabutin	Mycobutin

groups was 70%, 66% and 61%, respectively, at the 100 mg dosage, and 67%, 72% and 80% at the 150 mg dosage, with no difference seen between groups due to treatment duration. The SVR rate in relapsers was 85% for both the 100 mg and 150 mg dosages. On the other hand, the SVR rate for partial responders and null responders was 57% and 46%, respectively, at the 100 mg dosage of SMV, and 75% and 51% at the 150 mg dosage. This indicates that within the non-responders, a higher SVR rate is achieved in partial responders than in null responders. In particular, if we confine the analysis to genotype 1b, common in Japanese patients, the SVR rate for partial responders and null responders was 68% and 56%, respectively, at the 100 mg dosage of SMV, and 88% and 58% at the 150 mg dosage. In genotype 1a, the SVR rate for partial/null responders was 56%/33% at 100 mg and 42%/33% at 150 mg.[8]

Recommendations

- *The SVR rate in IFN-naïve subjects was significantly higher for SMV + Peg-IFN + RBV triple therapy than for Peg-IFN + RBV dual therapy for 48 weeks.*
- *A high SVR rate of 90–97% was achieved with SMV + Peg-IFN + RBV triple therapy in relapsers following previous IFN therapy.*
- *An SVR rate of 36–51% was achieved with SMV + Peg-IFN + RBV triple therapy in non-responders to previous IFN therapy.*
- *In an overseas trial, subanalysis of non-responders to previous IFN therapy showed a higher SVR rate in partial responders than in null responders, although there is no data available regarding Japanese subjects.*

2.2 Adverse reactions

In the CONCERT-1 trial,[9] the treatment completion rate was 92.7%. Only 4.9% of subjects in the triple therapy group discontinued treatment due to adverse events, as against 8.3% of subjects in the Peg-IFNα-2a + RBV dual therapy group, with no significant difference between groups.

Elevated bilirubin levels were seen in 40.7% of subjects administered SMV, but these were mild, transient increases not associated with elevated AST or ALT levels. Bilirubin levels in grade 1 (1.1–1.5 mg/dL) were seen in 25.2%, grade 2 (1.6–2.5 mg/dL) in 14.6%, and grade 3 (2.6–5.0 mg/dL) in 0.8%, with no cases of grade 4 (> 5.0 mg/dL). Elevated bilirubin levels are reported to be caused by inhibition of hepatic transporter activity by SMV.[15]

The type and incidence of adverse reactions, including anemia, skin conditions, renal dysfunction, hyperuricemia, malaise, and gastrointestinal symptoms, were similar for SMV + Peg-IFN + RBV triple therapy and for Peg-IFN + RBV dual therapy. The incidence and degree of anemia was similar for both treatment groups; for the SMV-based triple therapy group, the lowest hemoglobin level was ≥10.6 g/dL in 29.3% of subjects, grade 1 anemia (Hb 9.5–10.5 g/dL) in 41.5%, grade 2 anemia (8.0–9.4 g/dL) in 29.3%, and no cases of grade 3 anemia (<8.0 g/dL).

Skin conditions were reported in 57.7% of subjects, all grade 1 or 2, with similar incidences, degrees of severity, and discontinuation rates in the two treatment groups. No serious cutaneous reactions, such as Stevens-Johnson syndrome (SJS) or drug-induced hypersensitivity syndrome (DIHS), were reported.

Recommendations

- *A transient, mild elevation in bilirubin levels may be seen in patients undergoing SMV + Peg-IFN + RBV triple therapy, caused by inhibition of hepatic transporter activity.*
- *The type and incidence of other adverse reactions are similar to those seen with Peg-IFN + RBV dual therapy, yielding high completion rates.*

2.3 Drug interactions

Since SMV is mainly metabolized by CYP3A, co-administration with inhibitors or inducers of CYP3A may affect plasma levels of SMV. In particular, co-administration with strong inducers of CYP3A may enhance the metabolism and markedly lower plasma SMV levels, resulting in attenuating the therapeutic effects. As a result, co-administration of drugs listed in Table 1 is contraindicated.[16]

In addition, since SMV inhibits OATP1B1 and P-glycoprotein, co-administration with drugs transported through these channels may reduce plasma levels of those drugs. The package insert should be referred to before administrating SMV.

Recommendations

- *Since SMV is mainly metabolized by CYP3A and inhibits OATP1A1 and P-glycoprotein, co-administration of*

some drugs is contraindicated. The package insert should be referred to before administrating SMV.

2.4 Drug resistance

The CONCERTO-2 and CONCERTO-3 trials,[10] conducted with non-responders and relapsers, investigated gene mutations in the NS3 protease region in cases of treatment failure, including breakthrough, meeting the discontinuation criteria due to insufficient antiviral effect, HCV RNA positive at completion of treatment, and relapse following completion. Testing for genetic mutations was possible in 59 out of 61 cases of treatment failure, in 54 (92%) of whom mutations conferring SMV resistance were detected. Almost all of these were amino acid 168 substitutions (52/54), with 42 cases of substitution including D168V (35 single D168V substitutions, 7 mixed or multiple substitutions), and 10 single or mixed D168A/H/T/E/X substitutions. For the two cases with no D168 substitutions detected, a single Q80L substitution was seen in one, and mixed Q80K and R155K substitutions in the other. Genotype 1b was present in 97% of the subjects of these studies, and the overseas ASPIRE study also reported that D168V substitutions are responsible for almost all SMV resistance in genotype 1b, whereas R155K substitutions are mainly responsible for SMV resistance in genotype 1a.[17]

Overseas clinical trials have reported that the presence of Q80K polymorphism pretreatment in patients with genotype 1a may reduce the SVR rate.[8,12,13] As Q80K polymorphism is detected in 23–41% of patients with genotype 1a, this may be a predictive factor for therapeutic efficacy. Q80K polymorphism is rare in patients with genotype 1b.[8]

Recommendations

- *Resistant mutations are found in a high proportion of patients in whom SMV + Peg-IFN + RBV triple therapy is ineffective. Almost all of these mutations were D168V substitutions in genotype 1b.*
- *SVR rates may be reduced in patients with genotype 1a and Q80K polymorphism pretreatment. Q80K polymorphism is rare in patients with genotype 1b.*

3. TREATMENT-NAÏVE PATIENTS

A NUMBER OF new agents are under development for the treatment of HCV genotype 1 and high viral load (≥5.0 log IU/mL using real-time PCR, HCV core antigen ≥300 fmol/L) infections. These include HCV selective antiviral agents (protease inhibitors, polymerase inhibitors, NS5A inhibitors), new IFN preparations, RBV prodrugs, and agents with immunostimulant effects. At present, however, what we have available for general clinical use are antiviral therapies based on IFN preparations, in other words Peg-IFN (IFN) ± RBV ± protease inhibitors (SMV, TVR). In 2011 TVR + Peg-IFN + RBV triple therapy became available for use in Japan. Use of this combination reduced the duration of treatment for 48 or 72 weeks to 24 weeks, and provided a marked improvement in therapeutic efficacy, albeit some problems with adverse reactions. In December 2013, national medical insurance coverage approved the use of SMV,[9–11] a second generation protease inhibitor, for the treatment of genotype 1 high viral load infections. The duration of treatment for SMV + Peg-IFN + RBV triple therapy is 24 weeks, the same as for TVR-based triple therapy. However, once daily dosing for the former, as well as high SVR rates of 80–90% in Japanese clinical trials with treatment naïve subjects (DRAGON,[6] CONCERTO-1,[9] and CONCERTO-4[11]), and similar rates of adverse reactions to the control Peg-IFN + RBV dual therapy group, make SMV + Peg-IFN + RBV triple therapy the present treatment of first choice.

There are no clear discontinuation criteria for SMV-based triple therapy, and very few patients in whom this regimen is contraindicated, so in general the discontinuation criteria for TVR-based triple therapy should be followed.

In some patients, however, in whom adverse reactions are a concern, and the risk of carcinogenesis is considered low, it may be possible to await the introduction of the new agents with more favorable safety profiles.

3.1 Predictors of therapeutic efficacy of SMV-based combination therapy

3.1.1 IL28B

In the Japanese CONCERTO –1 trials using SMV-based combination therapy, subanalysis according to IL28B alleles (rs8099917 SNP) yielded an SVR24 rate of 94% (77/82) for the TT allele, and 78% (32/41) for the TG/GG alleles.[9] This represents a relatively high SVR rate for the TG or GG minor alleles achieved with SMV-based combination therapy, unlike Peg-IFN + RBV dual therapy, whose therapeutic efficacy is strongly affected by IL28B polymorphism (Fig. 4). A similar trend was seen in the CONCERTO-4 trial, with an SVR24 rate of 100% (16/16) for the TT allele, and 75% (6/8) for the TG/GG alleles, although subject numbers were small.[11]

In the overseas QUEST-1 and QUEST-2 trials using SMV-based combination therapy, SVR12 rates stratified

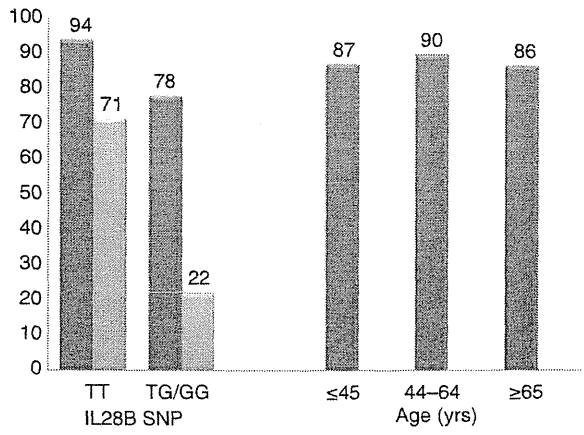

Figure 4 Results in treatment-naïve patients using the SMV + Peg-IFNα-2a + RBV triple therapy regimen; influence of IL28B polymorphism and age (CONCERTO-1 trial[9]). ■, SMV + Peg-IFNα-2a + RBV; ■, Peg-IFNα-2a + RBV.

for IL28B alleles (rs12979860 SNP) were 97% (72/77) and 96% (72/77) respectively for the CC allele, 76% (114/150) and 80% (114/142) for the CT allele, and 65% (24/37) and 58% (23/40) for the TT allele, showing a similar trend to the Japanese studies (Table 3).

3.1.2 Age and fibrosis

SVR24 rates stratified for age in the CONCERTO-1 trial were 87% (20/23) for subjects ≤ 45, 90% (70/78) for those aged 44–64, and 86% (19/22) for those ≥65. No clear differences were seen in SVR rates according to age for those ≤70 years old (Fig. 4). As for fibrosis, QUEST-1 and QUEST-2 examined the relationship between hepatic fibrosis and SVR12 rates, finding SVR12 rates of 83% and 85% respectively for F0-2, 78% and 67% for F3, and 58% and 65% for F4 (Table 3). These results suggest a correlation between the degree of hepatic fibrosis and the efficacy of SMV-based combination therapy. However, the classification F4 is not included in Japanese clinical trials, and there have been no reports of therapeutic results stratified for the degree of hepatic fibrosis.

Taken together, the results of Japanese and overseas clinical trials showed no clear age-related differences in therapeutic effect of SMV + Peg-IFN + RBV triple therapy. Although IL28B SNPs and the degree of fibrosis may influence therapeutic efficacy, SVR rates of 60–80% were still achieved in patients with IL28B minor alleles and advanced fibrosis ≥ F3. Accordingly, at present we cannot say that age, IL28B SNPs or the degree of fibrosis exerts any great influence on the therapeutic efficacy of this treatment regimen.

Recommendations

- *SMV + Peg-IFN + RBV triple therapy is at present the treatment of first choice in IFN-naïve patients.*
- *IL28B polymorphism has little influence on the SVR rate in IFN-naïve patients undergoing SMV + Peg-IFN + RBV triple therapy, with relatively high SVR rates achieved even in patients with the TG/GG minor alleles.*
- *In Japanese clinical trials conducted with subjects aged ≤ 70, no clear correlation could be identified between age and SVR rates.*
- *Although Japanese data is lacking, the results of overseas clinical trials indicate that advanced hepatic fibrosis may influence SVR rates.*
- *From the above, in general, if treatment is likely to be tolerated, SMV-based triple therapy is indicated in all patients who meet the criteria for antiviral therapy (ALT > 30 U/L or platelet count <150 000/μL), irrespective of IL28B SNP status.*
- *In some patients, however, in whom adverse reactions are a concern, and the risk of carcinogenesis is*

Table 3 Overseas results with SMV + Peg-IFN + RBV triple therapy; influence of IL28B polymorphism and age (SVR12, %) (QUEST-1,[12] QUEST-2[13] and PROMISE trials[14])

		IL28B SNP			Fibrosis (METAVIR)		
		CC	CT	TT	F0-2	F3	F4
QUEST-1	SMV+Peg-IFN+Rib	97	76	65	83	78	58
	Peg-IFN+Rib	78	42	24			
QUEST-2	SMV+Peg-IFN+Rib	96	80	58	85	67	65
	Peg-IFN+Rib	81	41	19			
PROMISE	SMV+Peg-IFN+Rib	89	78	65	82	73	74
	Peg-IFN+Rib	53	34	18			

considered low, it may be possible to await the introduction of the new agents with more favorable safety profiles.

3.2 Selection of antiviral therapy in treatment-naïve patients (Fig. 5)

3.2.1 Elderly patients

In this patient group at high risk of hepatocellular carcinogenesis, the best possible antiviral therapy should be promptly commenced. However, the possibility of adverse reactions, and the possibility that viral eradication may not be achieved, should be thoroughly explained to the patient in advance. Although the introduction of TVR + Peg-IFN + RBV triple therapy improved SVR rates in comparison to Peg-IFN + RBV dual therapy,[1] postmarketing surveys revealed serious adverse reactions in approximately 40% of elderly patients. Accordingly, it is recommended that TVR therapy should be commenced at a reduced dosage of 1500 mg/day,[18] although great caution is still required in its use in this age group. On the other hand, clinical trials of SMV + Peg-IFN + RBV triple therapy for treatment-naïve patients have reported an SVR rate of 86% (19/22) in elderly patients aged ≥ 65 (and ≤70), indicating a therapeutic efficacy similar to that seen in non-elderly patients (Fig. 4). Furthermore, very little difference is seen between SMV-based triple therapy and Peg-IFN + RBV dual therapy in terms of safety. Accordingly, SMV + Peg-IFN + RBV triple therapy should be commenced as soon as possible if treatment is likely to be tolerated.

If antiviral therapy is not introduced due to concerns about tolerability, and ALT levels are abnormal, protective therapy (stronger neo-minophagen C; SNMC and/or ursodeoxycholic acid; UDCA) should be commenced.[1] Long-term low dose Peg-IFN (IFN) therapy is another option.[1]

Recommendations

- *Elderly patients are at high risk of hepatocellular carcinogenesis, and should commence antiviral therapy promptly.*
- *SMV + Peg-IFN + RBV triple therapy is the antiviral treatment of first choice in treatment-naïve elderly patients.*
- *If antiviral therapy is not introduced and ALT levels are abnormal, protective therapy (SNMC, UDCA) should be commenced. Long-term low dose Peg-IFN (IFN) therapy is another option.*

3.2.2 Non-elderly patients

Although the risk of hepatocellular carcinogenesis is relatively low in non-elderly patients, the introduction of antiviral therapy is inevitably necessary in cases of advanced hepatic fibrosis, as in elderly patients. In general, SMV + Peg-IFN + RBV triple therapy should be administered to patients with advanced fibrosis. Also consider IFNβ + RBV combination therapy in patients with depressive symptoms.[1] The risk of carcinogenesis is considered lower in patients with mild fibrosis, so it may be reasonable to await the advent of newer agents with fewer adverse reactions. Determination of IL28B SNP status may be of benefit when the decision whether to commence treatment is a difficult one. However, as mentioned above, clinical trials of SMV + Peg-IFN + RBV triple therapy in treatment-naïve subjects reported SVR rates of approximately 80% in patients

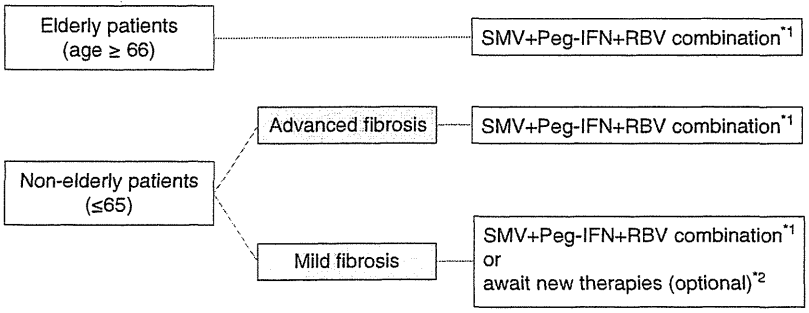

Figure 5 Treatment flow chart for treatment-naïve patients. Use IL28B testing as a reference if available. Follow therapy protocol for treatment-naïve patients if previous therapy was Peg-IFN (IFN) monotherapy or details of previous therapy with Peg-IFN (IFN) and RBV are unknown. Consider IFNβ + RBV combination if depressive symptoms present. *1 TVR + Peg-IFN + RBV triple therapy is another option (TVR should be commenced at a reduced dosage of 1500 mg/day in the elderly). *2 Protective therapy or low dose Peg-IFN(IFN) therapy if abnormal ALT levels.

with IL28B minor alleles (Fig. 4). SMV-based triple therapy should therefore be considered in all patients who meet the criteria for antiviral therapy (ALT > 30 U/L or platelet count < 150 000/μL)[1] if treatment is likely to be tolerated, irrespective of IL28B SNP status. If antiviral therapy is not introduced, and ALT levels are abnormal, protective therapy should be commenced.[1]

Recommendations

- *Although the risk of hepatocellular carcinogenesis is relatively low in non-elderly patients, the introduction of antiviral therapy is inevitably necessary in cases of advanced hepatic fibrosis, as in elderly patients. Waiting for advent of newer agents with fewer adverse reactions is an option in patients with mild fibrosis.*
- *In general, SMV + Peg-IFN + RBV triple therapy should be administered to treatment-naïve non-elderly patients with advanced fibrosis.*
- *Although treatment may be delayed in non-elderly patients with mild fibrosis, SMV-based triple therapy should be considered in all patients who meet the criteria for antiviral therapy (ALT > 30 U/L or platelet count < 150 000/μL) if treatment is likely to be tolerated. If antiviral therapy is not introduced, and ALT levels are abnormal, protective therapy should be commenced.*

4. PREVIOUSLY-TREATED CASES (RETREATMENT)

4.1 Predictors of therapeutic efficacy of SMV-based combination therapy

SEVERAL LINES OF clinical studies indicate that, in retreatment using SMV + Peg-IFN + RBV combination therapy, response to the previous treatment is the best indicator of the efficacy of retreatment when IFN/Peg-IFN + RBV combination therapy is ineffective.[10,11,17] In the overseas phase II trial (ASPIRE trial), administering SMV + Peg-IFN + RBV triple therapy to previously treated subjects, Peg-IFN + RBV combination therapy was administered for 48 weeks, in combination with SMV 100 mg or 150 mg/day for the first 12 or 24 weeks, or the entire 48 weeks. As described above, SVR rates for the different SMV dosages (100/150 mg/day) were 85%/85% in relapsers, 57%/75% in partial responders, and 46%/51% in null responders. No differences were seen in SVR rates according to dosage, whereas the response to previous therapy did influence SVR rates, with a greater therapeutic effect seen in partial responders than in null responders.[17] Similarly, in Japanese phase III trials (CONCERTO-2/3[10]) administering SMV + Peg-IFN + RBV triple therapy to previously treated subjects, SVR rates in relapsers and non-responders were 90% (44/49) and 51% (27/53), respectively (Fig. 3). In the CONCERTO-4[11] using Peg-IFNα-2b, the SVR rate was 97% (28/29) in relapsers, and 38% (10/26) in non-responders, a similar result to the CONCERTO-2/3[10] trials using Peg-IFNα-2a (Fig. 2).

Examination of the therapeutic efficacy of SMV-based combination therapy in relapsers, stratified for IL28B SNP status, revealed SVR24 rates of 91% (32/35) for the TT allele, and 86% (12/14) for the TG/GG alleles in the CONCERTO-3 trial (Fig. 6), and 96% (25/26) for the TT allele, and 100% (3/3) for the TG/GG alleles in the CONCERTO-4 trial. High SVR rates were achieved in relapsers in both studies, irrespective of IL28B SNP status. On the other hand, in the CONCERTO-2 trial,[10] conducted with non-responders, SVR24 rates stratified for IL28B SNP status were 50% (7/14) for the TT allele, and 42% (39/92) for the TG/GG alleles (Fig. 6), again showing no difference in SVR rates associated with IL28B polymorphism.

In the overseas PROMISE trial,[14] conducted with relapsers, SVR12 rates stratified for IL28B alleles (rs12979860 SNP) were 89% (55/62) for the CC allele, 78% (131/167) for the CT allele, and 65% (20/31) for the TT allele. Examination of the relationship between hepatic fibrosis and SVR12 rates yielded SVR12 rates of 82% for F0-2, 73% for F3, and 74% for F4 (Table 3). These results demonstrated that, unlike treatment-naïve cases, high SVR rates can be achieved irrespective of the

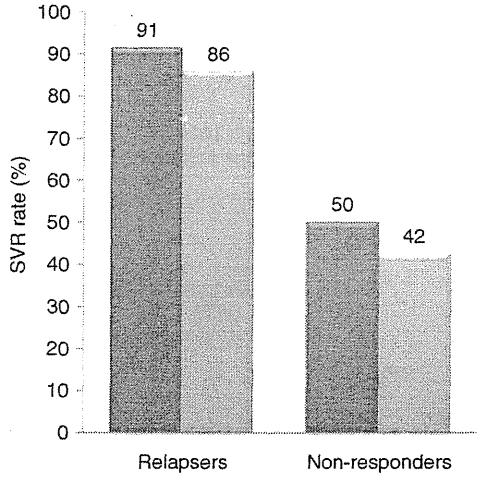

Figure 6 Results of treatment using SMV + Peg-IFNα-2a + RBV triple therapy in relapsers and non-responders depending on IL28B status (CONCERTO-2/3 trial[10]). ■, TT; ■, TG/GG.