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A prospective study on treatment of chronic hepatitis C with tailored and extended interferon-alpha regimens according to pretreatment virological factors

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Abstract

Hepatitis C virus genotype and viral loads are important predictors for sustained virologic response (SVR) to interferon-alpha therapy for chronic hepatitis C (CHC). We have conducted a prospective study on treatment of 90 patients with a tailored-dose and extended interferon-alpha regimen according to pretreatment virologic factors (low-risk, genotype non-1b/viral loads $\leq$ 0.65 Meq./ml, 6 million units thrice weekly for 12 weeks (6 MU $\times$ 12 weeks) followed by 3 MU $\times$ 24 weeks; high-risk, genotype 1b/viral loads $>$ 0.65 Meq./ml, 6 MU $\times$ 24 weeks followed by 3MU $\times$ 24 weeks; medium-risk, the others, 6MU $\times$ 12 weeks followed by 3 MU $\times$ 36 weeks), and compared to 123 patients with fixed-dose regimen (6 MU $\times$ 24 weeks). Patients with tailored-dose regimen had a significantly higher rate of SVR than those receiving fixed-dose interferon-alpha (46.7% versus 29.3%, $P < 0.01$, intention-to-treat analysis). Improved efficacy was mainly seen in the medium-risk (48.9% versus 26.6%, $P = 0.02$) and the high-risk groups (26.1% versus 8.3%, $P = 0.06$), but not in the low-risk group. By using multivariate logistic regression, low pretreatment viral loads and tailored-dose IFN regimens were significantly associated with higher SVR in both the high- and medium-risk groups. There were no differences in the tolerability and in the incidence of adverse effects between fixed-dose and tailored-dose groups. In conclusion, our results demonstrate the efficacy of tailored-dose interferon-alpha therapy for CHC; these could provide decision-making information for standard/pegylated interferon-alpha combining ribavirin therapy according to baseline predictors.

Keywords: Chronic hepatitis C; Dose; HCV; Interferon; Predictor; Tailored

1. Introduction

Hepatitis C virus (HCV) is the major etiologic agent in parenterally transmitted non-A non-B hepatitis and frequently causes persistent infection leading to chronic liver disease and primary hepatocellular carcinoma (HCC) (Alter et al., 1992; Lauer and Walker, 2001). Interferon-alpha (IFN-α) was the first approved therapy in the 1980s, although it resulted in a sustained virological response in only 8–20% of chronic hepatitis C patients treated with a standard regimen of IFN-α monotherapy, 3 million units (MU) thrice weekly for 24 weeks (Poynard et al., 1996; Carithers and Emerson, 1997; Thevenot et al., 2001). A number of factors have been considered in terms of their potential to predict the response to IFN-α therapy. These include infection with HCV genotype 1b, higher levels of viremia and the presence of cirrhosis, which have been reported to be associated with a worse response (Lauer and Walker, 2001; Shiratori et al., 1997; Yu et al., 1999, 2000). Improvement of efficacy on chronic hepatitis C could be achieved with higher dose and/or longer duration of IFN therapy (Poynard et al., 1996; Carithers and Emerson, 1997; Thevenot et al., 2001). Since HCV genotype and baseline viral loads are important predictors for sustained virologic response (SVR) to IFN-α, we divided patients into three virologically unfavorable risk groups according to the infected HCV genotype and pretreatment HCV RNA levels based on the best cut-off for predicting response to IFN in Taiwanese chronic

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hepatitis C patients treated with IFN 6 MU thrice weekly for 24 weeks (Yu et al., 1999) and treated them prospectively with a tailored-dose IFN regimen.

Since 1995, we have treated a number of Taiwanese patients with chronic hepatitis C with a fixed-dose IFN regimen, 6 MU thrice weekly for 24 weeks, and since 1997, with either fixed-dose or tailored-dose IFN regimens according to virologic risk factors. The present study was conducted before ribavirin became available in Taiwan. We report herein the results of both IFN regimens, as well as the effect of a number of relevant factors affecting the SVR.

2. Materials and methods

2.1. Patients

Two hundred and thirteen histologically proven naïve chronic hepatitis C patients, including 125 males and 88 females, aged between 18 and 65 years (mean 45.1 ± 11.7 years), were enrolled in the study. All were positive for HCV antibodies (second-generation, enzyme-linked immunosorbent assay, Abbott, North Chicago, IL, USA), elevated serum levels of alanine aminotransferase (ALT) and serum HCV RNA for at least 6 months. Patients with concurrent hepatitis B virus, alcohol abuse (≥80 ml ethanol per day), overt hepatic failure, a current or past history of psychiatric condition, pregnancy, or evidence of hepatocellular carcinoma, were excluded. Two pathologists assessed all biopsy results, which were taken before IFN-α treatment, without knowledge of patients' clinical or laboratory data. Disease activity grade and fibrosis stage were quantitatively scored according to the histological activity index (Knodell et al., 1981). A follow-up liver biopsy was performed in 76 patients. The present study was approved by the ethics committee of Kaohsiung Medical University Hospital. After they had given their informed consent, all patients were treated with recombinant IFN-α-2a ($n = 55$), IFN-α-2b ($n = 92$) or lymphoblastoid IFN-α-n1 ($n = 66$), given intramuscularly. One hundred and twenty-three patients received fixed-dose IFN treatment (IFN 6 MU thrice weekly for 24 weeks). Ninety patients were treated with tailored-dose IFN regimens according to the virological risk factors regimens: low-risk group, genotype non-1b/viral loads ≤ 0.65 Meq./ml, 6 MU thrice weekly for 12 weeks, followed by 3 MU thrice weekly for 24 weeks; high-risk group, genotype 1b/viral loads > 0.65 Meq./ml, 6 MU thrice weekly for 24 weeks, followed by 3 MU thrice weekly for 24 weeks; medium-risk group, the others, 6 MU thrice weekly for 12 weeks, followed by 3 MU thrice weekly for 36 weeks (Table 1). Group allocation was chronological and consecutive rather than randomized, because, before 1997, most patients were given a fixed 6-MU IFN-α regimen and then a tailored IFN-α regimen prospectively. The presence of HCV RNA in the serum was assessed every three months during the IFN treatment period and follow-up period. Sustained virological responder (SVR) was defined as patients showing clearance of HCV RNA by at the end-of-treatment and 12 months after end-of-treatment. The others were classified as non-SVR. Histological improvement and worsening was defined as a ≥2-point decrease and increase in the total necroinflammatory scores between paired biopsies, respectively.

2.2. Detection/quantification of serum HCV RNA and genotyping

Detection of serum HCV RNA was performed using a standardized automated qualitative reverse transcription polymerase-chain-reaction assay (RT-PCR, COBAS AMPLICOR Hepatitis C Virus Test, Version 2.0; Roche, Branchburg, NJ, USA; lower limit of detection, 100 copies (50 IU) per ml). HCV genotypes 1a, 1b, 2a, 2b and 3a were determined by amplification of the core region using genotype-specific primers described by Okamoto et al. (1993). Serum HCV RNA levels were measured using the branched DNA assay (Quantiplex HCV RNA 2.0, Bayer, Emeryville, CA, USA; quantification range, 0.2–120 Meq./ml), performed strictly in accordance with the manufacturer's instructions.

2.3. Statistical analyses

Frequency was compared between groups using the chi-square test with Yates' correction or Fisher's exact test.

Table 1
The tailored- and fixed- interferon regimens for chronic hepatitis C patients according to the status of virological factors

	HCV RNA (genotype/pretreatment levels)	Patient number	Interferon regimens (thrice weekly)			
			Weeks 1–12 (MU)	Weeks 13–24 (MU)	Weeks 25–36 (MU)	Weeks 37–48 (MU)
High-risk group ($n = 59$)	1b/>0.65 Meq./ml	Fixed = 36	6	6	–	–
		Tailored = 23	6	6	3	3
Medium-risk group ($n = 109$)	(1) Non-1b/>0.65 Meq./ml or (2) 1b/≤0.65 Meq./ml	Fixed = 64	6	6	–	–
		Tailored = 45	6	3	3	3
Low-risk group ($n = 45$)	Non-1b/≤0.65 Meq./ml	Fixed = 23	6	6	–	–
		Tailored = 22	6	3	3	–

Note: Meq., million equivalents; MU, million units.

Group means were compared using Student's *t*-test. Serum HCV RNA levels were expressed as the mean ± standard deviation after logarithmic transformation of original values. Stepwise logistic regression was used to analyze factors associated with response to IFN-α. Comparisons of paired liver histology were carried out with two-sample Wilcoxon's signed rank test. All procedures were performed by using the package SAS statistical software (SAS Institute, Cary, NC, USA).

3. Results

3.1. SVR

Total 123 patients received fixed-dose IFN-α therapy, including 36 in the high-risk virologic group, 64 in the medium-risk and 23 in the low-risk groups; 90 received a tailored-dose IFN-α regimen, including 23 in the high-risk, 45 in the medium-risk and 22 in the low-risk groups. All were followed-up for at least 12 months after the end of treatment. Baseline clinical and laboratory data were not different between the fixed and tailored IFN-α regimen in the medium- and low-risk groups (Table 2). In the high-risk group, the pretreatment levels of serum HCV RNA was significantly higher in the tailored-dose IFN-α group than in fixed-dose IFN-α group (6.89 ± 0.50 logs versus 6.41 ± 0.45 logs, $P < 0.01$).

Based on intention-to-treat analysis, 42 of 90 patients (46.7%) with tailored-dose IFN-α treatment achieved SVR, which was significantly higher than those with fixed-dose IFN-α (36/123, 29.3%, $P < 0.01$, Fig. 1). The rate of SVR in the low-, medium-, and high-risk groups was 69.6, 26.6, and 8.3%, respectively, for patients treated with fixed-dose IFN-α ($P < 0.001$, chi-square test with linear trend), in contrast to 63.6, 48.9, and 26.1%, respectively, for those receiving tailored-dose IFN-α regimen (low-risk group versus medium-risk group, no difference; medium-risk group versus high-risk group, $P = 0.07$; low-risk group versus high-risk group, $P < 0.05$). With regard to the virologic risk group, the rate of SVR in the high-risk group was higher for patients with a tailored regimen than for those with a fixed regimen (26.1% versus 8.3%, $P = 0.06$, borderline significance). The difference became significant after controlling for the confounding factor, pretreatment HCV RNA levels ($P < 0.05$). The rate of SVR in the medium-risk group was significantly higher for patients with tailored regimen than for those with fixed regimen (48.9% versus 26.6%, $P = 0.02$). The rate of SVR in the low-risk group did not differ between the tailored- and fixed-dose regimens.

3.2. Factors predicting SVR

The independent predictive value of age, sex, history of transfusion, necroinflammatory activity and fibrosis of liver histopathology, pretreatment serum levels of alanine aminotransferase and HCV RNA, HCV genotype, IFN preparations and regimens (fixed regimens versus tailored regimens) for the achievement of SVR was determined by using stepwise logistic regression analysis (Table 3). The significant factors associated with SVR in 213 patients were pretreatment HCV RNA levels, HCV genotype (1b versus non-1b)

Table 2
Baseline demographic and clinical features of chronic hepatitis C patients treated with fixed and tailored interferon-alpha regimens according to virological risk factors[a]

	High-risk group[a] (number (%))		Medium-risk group[a] (number (%))		Low-risk group[a] (number (%))	
	Fixed-dose IFN regimen	Tailored-dose IFN regimen	Fixed-dose IFN regimen	Tailored-dose IFN regimen	Fixed-dose IFN group	Tailored-dose IFN group
Patient number	36	23	64	45	23	22
Gender (male/female)	20/16	16/7	38/26	30/15	11/12	10/12
Age (year)	45.0 ± 11.6	43.4 ± 14.5	46.6 ± 11.4	44.0 ± 10.9	44.6 ± 12.3	44.8 ± 12.3
History of transfusion	10(27.8)	7(30.4)	16(25.0)	10(22.7)	8(34.8)	8(36.4)
Liver histopathology						
Necroinflammatory activity (score > 3)	22(61.1)	13(56.5)	34(53.1)	26(57.8)	17(73.9)	15(68.2)
Fibrosis (score 3 or 4)	10(27.8)	5(21.7)	10(15.6)	7(15.6)	7(30.4)	4(18.2)
Pretreatment ALT value (IU/l)	102.8 ± 79.6	81.9 ± 46.4	110.0 ± 98.0	118.6 ± 85.7	100.2 ± 63.3	141.5 ± 253.7
HCV RNA level (log eq./ml)	6.41 ± 0.45[b]	6.89 ± 0.50[b]	6.20 ± 0.72	6.43 ± 0.77	5.42 ± 0.27	5.25 ± 0.32
HCV genotype 1b	36(100)	23(100)	21(32.8)	9(20.0)	0	0
Interferon preparation						
Recombinant IFN-α-2a	6(16.7)	4(17.4)	18(28.1)	10(22.2)	10(43.5)	7(31.8)
Recombinant IFN-α-2b	19(52.8)	12(52.2)	25(39.1)	19(42.2)	8(34.8)	9(40.9)
Lymphoblastoid IFN-α-n1	11(30.6)	7(30.4)	21(32.8)	16(35.6)	5(21.7)	6(27.3)

[a] Low-risk group, neither genotype 1b nor pretreatment HCV RNA levels > 0.65 Meq./ml; medium-risk group, either genotype 1b or pretreatment HCV RNA levels > 0.65 Meq./ml; high-risk group, both genotype 1b and pretreatment HCV RNA levels > 0.65 Meq./ml.

[b] $P < 0.01$, significantly different.

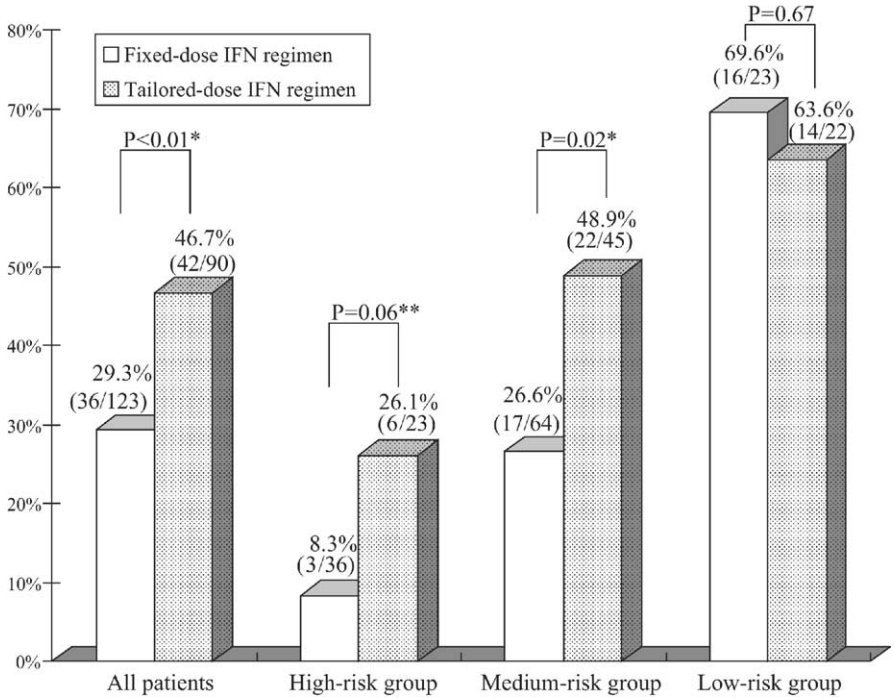

Fig. 1. Intention-to-treat analysis of sustained virological response (SVR) for chronic hepatitis C patients treated with fixed and tailored interferon-alpha regimens according to virological risk factors. Low-risk group, neither genotype 1b nor pretreatment HCV RNA levels > 0.65 Meq./ml; medium-risk group, either genotype 1b or pretreatment HCV RNA levels > 0.65 Meq./ml; high-risk group, both genotype 1b and pretreatment HCV RNA levels > 0.65 Meq./ml. *Significant difference; **borderline significance.

and IFN regimens (fixed versus tailored). With regard to the virologic risk groups, pretreatment HCV RNA levels and IFN regimens were significantly associated with SVR in both high- and medium-risk groups. No factor was found to be associated with SVR in the low-risk group.

3.3. Discontinuation and adverse effect

The incidence of discontinuation of IFN therapy did not differ between fixed-dose group (10/123, 8.1%) and tailored-dose group (9/90, 10.0%, Table 4). In the tailored-dose group, two withdrew during weeks 25–48 due to an insufficient response or economic problem, respectively. There was also no difference of incidence of adverse events between fixed- and tailored-dose groups during weeks 1–12, as well as after week 12.

3.4. Paired histological examination

A follow-up liver biopsy was performed 1.0–5.3 years (mean ± S.D., 1.66 ± 0.84 years) after initiation of treatment in 76 patients. Histological improvement with a significant

Table 3
Multivariate logistic regression analysis of factors associated with sustained virological response for chronic hepatitis C patients treated with fixed and tailored interferon-alpha regimens according to virological risk factors

Group	Variables	Odds ratio	95% confidence interval	*P*-value
All patients				
Pretreatment HCV RNA levels	Per 1 log increase	0.296	0.184–0.477	<0.0001
HCV genotype	1b = 1; non-1b = 0	0.253	0.121–0.527	<0.001
Interferon regimen	Tailored = 1; fixed = 0	2.204	1.136–4.277	<0.05
Age	Per 1 year increase	0.982	0.955–1.011	0.056
High-risk group[a]				
Pretreatment HCV RNA levels	Per 1 log increase	0.135	0.016–0.910	<0.05
Interferon regimen	Tailored = 1; fixed = 0	7.467	1.008–55.321	<0.05
Medium-risk group[b]				
Pretreatment HCV RNA levels	Per 1 log increase	0.563	0.319–0.991	<0.05
Interferon regimen	Tailored = 1; fixed = 0	3.068	1.316–7.155	<0.01

[a] High-risk group, both genotype 1b and pretreatment HCV RNA levels > 0.65 Meq./ml.
[b] Medium-risk group, either genotype 1b or pretreatment HCV RNA levels > 0.65 Meq./ml.

Table 4
Incidence of discontinuation and adverse events

Variable	Fixed-dose IFN group, $n = 123$ (number (%))		Tailored-dose IFN group, $n = 90$ (number (%))	
	Weeks 1–12	Weeks 13–24	Weeks 1–12	Weeks 13–48[a]
Discontinuation	10 (8.1)		9 (10.0)	
	7 (5.7)	3 (2.4)	5 (5.6)	3 (3.3)
Adverse event	5 (4.1)	2 (1.6)	4 (4.4)	1 (1.1)
Insufficient response	0 (0)	1 (0.8)	0 (0)	1 (1.1)
Laboratory abnormality	1 (0.8)	0 (0)	1 (1.1)	0 (0)
Economic problem	1 (0.8)	0 (0)	0 (0)	1 (1.1)
Adverse event				
Flu-like symptoms[b]	79 (64.2)	34 (27.6)	57 (63.3)	22 (24.4)
Gastrointestinal manifestations[c]	32 (26.0)	5 (4.1)	24 (26.7)	6 (6.6)
Psychological manifestations[d]	67 (54.5)	52 (42.3)	45 (50.0)	31 (34.4)
Alopecia	25 (20.3)	91 (74.0)	22 (24.4)	56 (62.2)
Dermatological manifestations[e]	15 (12.2)	10 (8.1)	12 (13.3)	6 (6.6)

[a] For low virologic risk group, only weeks 13–36.
[b] Including fatigue, headache, pyrexia, myalgia, and rigors.
[c] Including nausea, vomiting, anorexia, and diarrhea.
[d] Including irritability, depression, and insomnia.
[e] Including dermatitis, and pruritus.

decrease in the mean scores for all necroinflammatory activity (periportal, intralobular, portal inflammation and total necroinflammatory score) was observed in the follow-up biopsy (Table 5). With regard to IFN regimens, both of the groups had a significantly histological improvement at the follow-up biopsy. The necroinflammatory activity improved in 65.4% ($n = 17$), remained stable in 30.8% ($n = 8$), and worsened in 3.9% ($n = 1$) of those patients that achieved a SVR ($n = 26$), in contrast to 48.0% ($n = 24$), 38.0% ($n = 19$), and 14.0% ($n = 7$), respectively, for the non-SVR ($n = 50$).

3.5. Long-term follow-up for viral status and incidence of cirrhosis and HCC

During a mean follow-up period of 5.07 years (0.88–8.61 years), reappearance of serum HCV RNA was found in three patients, one was a sustained responder in the fixed-dose group and two in the tailored-dose group, at the 57th, 48th, and 55th month, respectively. The durability of SVR was 97.2 and 95.2% for fixed- and tailored-dose groups, respectively.

Of 130 non-responders in the present study, 54 received second course of IFN treatment. Four of nine (44.4%) with IFN-α monotherapy and 26 of 45 (57.8%) with IFN-α/ribavirin combination therapy achieved second SVR. Clinical evaluation, liver biochemistry, α-fetoprotein, and abdominal sonography were performed every 3–6 months for patients without baseline cirrhosis, and every 2–3 months for those with baseline cirrhosis during the follow-up period.

For 180 baseline non-cirrhotic patients, 4 of 85 (4.7%) non-responders and 3 of 95 (3.2%) sustained responders progressed to cirrhosis during a mean follow-up period of 4.12 and 5.48 years, respectively. The incidence density of cirrhosis was 95 and 48.3 per 100 000 person-years for non-responders and sustained responders, respectively. The difference was not significant by using Kaplan–Meier survival analysis. In 1043.7 person-years of follow-up, HCC was detected in 7 of 100 (7%) non-responders and 3 of

Table 5
Mean liver histological scores before and after interferon-alpha treatment in 76 Taiwanese chronic hepatitis C patients

	Before treatment	Follow-up[a]	*P*-value[b]
Periportal inflammation	1.09 ± 1.41	0.64 ± 1.07	0.0218
Intralobular necrosis	0.77 ± 1.00	0.23 ± 0.67	0.0001
Portal inflammation	2.09 ± 1.25	1.17 ± 1.26	<0.0001
Total necroinflammatory score	3.92 ± 2.51	2.07 ± 2.39	<0.0001
Fibrosis	1.19 ± 1.20	1.01 ± 1.28	0.1686
Total necroinflammatory score			
Fixed-dose group ($n = 51$)	3.88 ± 2.60	2.06 ± 2.47	0.0004
Tailored-dose group ($n = 25$)	4.00 ± 2.38	2.08 ± 2.27	0.011

[a] Mean follow-up time was 1.66 ± 0.84 year (range 1.0–5.3 years) from initiation of treatment.
[b] Wilcoxon's signed rank test.

106 (2.8%) sustained responders. The incidence density of HCC was 136 and 42.5 per 100–000 person-years for non-responders and sustained responders, respectively. The difference was significant by using Kaplan–Meier survival analysis ($P < 0.05$).

4. Discussion

We have carried out the first prospective study on the efficacy of tailored-dose IFN-α therapy in a group of Taiwanese patients with chronic hepatitis C according to pretreatment virologic predictors. Overall, tailored-dose IFN-α regimen was significantly more effective (2.2-fold) than fixed-dose of IFN-α, 6 MU thrice weekly for 24 weeks based on intention-to-treat analysis. Improved efficacy was mainly seen in subgroups of patients with disease generally considered to be potentially IFN-resistant, the medium- and high-risk groups in the current study.

Treatment with IFN-α was the first approved therapy but a SVR could be achieved in only 8–20% of chronic hepatitis C patients treated with a standard regimen of IFN-α monotherapy (3 MU thrice weekly for 24 weeks) (Poynard et al., 1996; Carithers and Emerson, 1997; Thevenot et al., 2001). Therefore, how to improve the efficacy of IFN-α therapy is the concern of many studies. In our previous study, we have demonstrated that a fixed 6-MU IFN-α regimen (thrice weekly for 24 weeks) had greater effect than a 3-MU regimen (thrice weekly for 24 weeks) on SVR for naïve chronic hepatitis C patients with a rate of 37.1 and 23.7%, respectively (unpublished data). Analyzing the efficacy of dose-effect of IFN on virologic risk factors, HCV genotype and pretreatment viral levels based on the cut-off calculated in previous study on Taiwanese patients (Yu et al., 1999), we found that 6-MU regimen had better efficacy than 3-MU regimen for end-of-treatment virologic response (ETVR) in all three risk groups. However, the dose-effect on SVR could only be observed in the medium-risk group, but not in the low- and high-risk groups. Because the ETVR could be achieved in more than two-third of patients in all three groups, we therefore designed the tailored-dose IFN regimen for patients with different virologically unfavorable predictor(s) before ribavirin had become available in Taiwan, aiming at reducing the relapse rate after cessation of treatment. Six million units IFN thrice weekly was applied in the first 12 weeks for all three groups because high-dose IFN as well as induction therapy could result in early clearance of HCV viremia, which is very important in the prediction of IFN response (Yu et al., 2000; Neumann et al., 1998; Layden, 1999). Extended treatment improved SVR by reducing the relapse rate after the end of treatment (Poynard et al., 1996; Carithers and Emerson, 1997; Thevenot et al., 2001). For low-risk group, thus, we extended the IFN regimen from 24 to 36 weeks with the same total IFN dosage. For the medium- and high-risk groups, IFN regimens were extended to 48 weeks with higher total IFN dosage. However, the improvement of SVR by using the tailored-dose IFN regimen was mainly observed in the medium- and high-risk groups with an odd ratio (CI) of 3.068 (1.316–7.155) and 7.467 (1.008–55.321), respectively. The SVR was not improved by using tailored regimen for the low-risk group in the present study. These results implicate that combination therapy of IFN-α/pegylated IFN-α plus ribavirin (McHutchison et al., 1998; Manns et al., 2001) rather than extended therapy may have a greater efficacy in the treatment of patients with low viral load and genotype non-1b infection, as recommended in the consensus on management of chronic hepatitis C (Consensus, 2000; EASL, 1999). Although tailored-dose and extended IFN regimen could much improve the SVR for chronic hepatitis C patients with high viral load and genotype 1 infection in the present study as well as in previous reports (Iino et al., 2002; Arase et al., 2003), the efficacy remained unsatisfactory. Extended combination therapy with IFN-α/pegylated IFN-α plus ribavirin might be suggested for these patients.

In accordance with previous reports (Lauer and Walker, 2001; Shiratori et al., 1997; Yu et al., 1999, 2000; Martinot-Peignoux et al., 1998), we confirmed the associations of pretreatment serum HCV RNA levels, HCV genotype 1b and age with response to IFN-α treatment in chronic hepatitis C patients by using stepwise logistic regression model. After adjustment for the confounding factors by using logistic regression model, we could predict a 2.2-fold increase in probability for SVR to occur in the tailored-dose IFN regimen versus the fixed-dose IFN regimen. Consistent with previous studies (Poynard et al., 1995; Marcellin et al., 1997; Shiratori et al., 2000), a significant decrease in necroinflammatory activity of liver histology was observed in the current study. However, our material was unable to show whether the IFN treatment resulted in cessation of fibrogenesis, regardless of IFN regimen and virological response (data not shown). Indeed, no firm conclusion can be drawn about whether the fibrosis remaining at long-term follow-up was irreversible or whether it would diminish with even longer follow-up (Shiratori et al., 2000). Nevertheless, our results confirm that IFN therapy, when associated with SVR, reduces the incidence of HCC among chronic hepatitis C patients (Yoshida et al., 1999).

Similar to other reports (Larghi et al., 1998), the long-term viral response was excellent in this well-defined material of SVR. Serum HCV RNA was persistently undetectable in over 95% patients with SVR, whatever the IFN regimens. All the three patients, who had reappearance of serum HCV RNA, had concomitant flare of serum ALT, including two with ALT value above 10 times of the upper normal limit and one with ALT value above 3 times the upper normal limit. The first one is a resident of an HCV hyperendemic area, Tzukuan (Yu et al., 2001). The second patient had a history of blood transfusion due to a traffic accident 3 months before reappearance of HCV RNA and flare of ALT. The third patients had a history of dental procedure 4 months before reappearance of HCV RNA. Whether this is reinfection (Kao

et al., 2001) or recurrence (Larghi et al., 1998) of HCV remains to be clarified by phylogenetic analysis of the viral genome.

A greater efficacy in treatment of chronic hepatitis C was observed in combination with IFN-α and ribavirin (McHutchison et al., 1998), which has been available in Taiwan since August 1998 and is recommended for chronic hepatitis C patients (Consensus, 2000; EASL, 1999). More recently, combination of pegylated IFN-α plus ribavirin proved to be more effective and convenient and may replace the current standard of IFN-α plus ribavirn (Manns et al., 2001; Fried et al., 2002). The results of current study could provide decision-making information for future therapeutic strategies of individualizing dose and duration of standard or pegylated IFN-α treatment in combination with ribavirin according to the baseline virological predictors to improve the efficiency of HCV eradication. Longer duration and/or higher dose of pegylated IFN-α and ribavirin combination therapy is suggested for patients with genotype 1b infection and high viral load, as recommended in a recent consensus on management of chronic hepatitis C (Consensus, 2000; EASL, 1999; Di Bisceglie and Hoofnagle, 2002). However, pegylated IFN-α and ribavirin combination therapy is expensive and might carry potential side effects. The present tailored-dose regimen of IFN monotherapy might be suggested for patients who had higher viral load and/or with HCV genotype 1b infection and are contraindicated to receiving ribavirin and/or pegylated IFN-α therapy (Keating and Curran, 2003).

In conclusion, our study supports the conclusion that tailored-dose IFN regimen according to pretreatment virologic factors has better efficacy than fixed-dose 6-MU regimen, and is as tolerable as fixed-dose 6-MU regimen for chronic hepatitis C patients. Since pretreatment HCV RNA levels and genotype are unchangeable, adjustment of IFN dose and/or duration according to the unfavorable factors is important to achieve a better efficacy/risk ratio. Our results could provide decision-making information for future therapeutic strategies of dose and duration of standard or pegylated IFN-α plus ribavirin treatment according to baseline predictors (Di Bisceglie and Hoofnagle, 2002). In patients who are contraindicated to ribavirin and/or pegylated IFN, a tailored-dose regimen of standard IFN might be recommended for those with unfavorable virologic factor(s).

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