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Acta Medica Okayama

Volume 57, *Issue* 3 2003 *Article* 7

JUNE 2003

Efficacy of interferon retreatment on interferon-resistant patients with chronic hepatitis C.

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Efficacy of interferon retreatment on interferon-resistant patients with chronic hepatitis C.*

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Abstract

Chronic Hepatitis C can progress to end-stage liver cirrhosis or hepatocellular carcinoma. Interferon (IFN) therapy is effective in clearing the hepatitis C virus and in improving liver histology, however, few patients maintain a sustained response (SR) after IFN withdrawal. Immediate retreatment with IFN is therefore considered to be both effective and necessary, especially for patients who do not respond to the initial course of IFN therapy. All 145 patients included in the present study underwent liver biopsy, followed by a first treatment course with various IFNs (alpha2a, alpha2b, alpha, OIF or beta). If hepatitis C virus (HCV) RNA was positive after the first treatment, the patient was assigned to one of 3 groups, depending on whether his or her alanine transaminase (ALT)level was normalized (incomplete response, IR), partially responsive(PR), or non-responsive (NR). After an observational interval of 6 to 76 months, a second IFN treatment was initiated with a higher dose or the same dose of the same IFN for the IR group, and with a different IFN for the PR and NR groups. At 6 months after retreatment with IFN, the overall efficacy of the retreatment was 29.7.% In the case of the IR group, who received the same IFN, the overall efficacy was 45.2%. In patients identified as non-SR after the first treatment, who received a different type of IFN for retreatment, the overall efficacy was 18.6%. Anti-IFN antibody was not detected in most of the breakthrough cases. For some IR patients, retreatment with the same IFN was effective. Anti-IFN antibody was mostly negative, indicating that the same IFN can be used in both the first treatment and retreatment to obtain an SR. Switching to a different IFN was effective for some PR and NR patients, suggesting that changing IFN for such cases is a good therapeutic choice.

KEYWORDS: chronic hepatitis C, HCV RNA, breakthrough, IFN anitibody, retreatment with IFN

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*PMID: 12908013 [PubMed - indexed for MEDLINE]
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Acta Med. Okayama, 2003
Vol. 57, No. 3, pp. 151-158
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Acta Medica Okayama
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Original Article

Efficacy of Interferon Retreatment on Interferon-resistant Patients with Chronic Hepatitis C

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Chronic Hepatitis C can progress to end-stage liver cirrhosis or hepatocellular carcinoma. Interferon (IFN) therapy is effective in clearing the hepatitis C virus and in improving liver histology, however, few patients maintain a sustained response (SR) after IFN withdrawal. Immediate retreatment with IFN is therefore considered to be both effective and necessary, especially for patients who do not respond to the initial course of IFN therapy. All 145 patients included in the present study underwent liver biopsy, followed by a first treatment course with various IFNs (α2a, α2b, α, OIF or β). If hepatitis C virus (HCV) RNA was positive after the first treatment, the patient was assigned to one of 3 groups, depending on whether his or her alanine transaminase (ALT) level was normalized (incomplete response, IR), partially responsive (PR), or non-responsive (NR). After an observational interval of 6 to 76 months, a second IFN treatment was initiated with a higher dose or the same dose of the same IFN for the IR group, and with a different IFN for the PR and NR groups. At 6 months after retreatment with IFN, the overall efficacy of the retreatment was 29.7%. In the case of the IR group, who received the same IFN, the overall efficacy was 45.2%. In patients identified as non-SR after the first treatment, who received a different type of IFN for retreatment, the overall efficacy was 18.6%. Anti-IFN antibody was not detected in most of the breakthrough cases. For some IR patients, retreatment with the same IFN was effective. Anti-IFN antibody was mostly negative, indicating that the same IFN can be used in both the first treatment and retreatment to obtain an SR. Switching to a different IFN was effective for some PR and NR patients, suggesting that changing IFN for such cases is a good therapeutic choice.

Key words: chronic hepatitis C, HCV RNA, breakthrough, IFN antibody, retreatment with IFN

The treatment of chronic hepatitis C is a challenge for most hepatologists because it can easily progress to end-stage liver cirrhosis or hepatocellular carcinoma. Since the first discovery of Interferon (IFN)-α, a cytokine produced after stimulation of leukocytes or fibroblasts with virus infection or nucleotide treatment, growing numbers of subtypes of IFN have been identified [1]. Of these, IFN-α and IFN-β species have been used in the treatment of hepatitis. IFN therapy is an effective method of clearing the hepatitis C virus (HCV) from serum, normalizing biochemical liver function and improving liver histology in chronic hepatitis C patients. Nevertheless, only about 40% of patients respond to this therapy and up to 60% of responders show reactivation of the disease after IFN withdrawal [2-4]. In some cases the disease even reactivates during treatment, thus leading to 'breakthrough' status (BT). This lowers the

Received September 11, 2002; accepted January 23, 2003.
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ratio of sustained response (SR) to below 20%, as defined by normal serum alanine transaminase (ALT) levels and undetectable HCV RNA levels at 6 to 12 months after the end of therapy [3–6]. Immediate retreatment with IFN is therefore considered to be effective and necessary especially for patients who do not respond to the initial course of IFN therapy or who suffer a relapse of the disease. This refractoriness may be due to the acquisition of resistance to the therapy (*e.g.* occurrence of anti-IFN antibody, *etc.*), or from a total lack of response to IFN [7, 8]. Although controversial, some reports suggest a possible correlation between anti-IFN antibody and the incidence of breakthrough [6–9]. Retreatment with the same IFN could therefore possibly result in another failure to respond. Thus, it is naturally speculated that the usage of different types of IFN may be beneficial for retreatment of non-responders (NR). On the other hand, growing numbers of reports suggest that some NR or relapsing patients can be successfully treated with a second cycle of the same IFN [10–12]. Previous studies show that the SR rate for retreated patients with a 6-month course of IFN-α is 20 % to 40% in cases of relapsers [10, 11, 13, 14], up to 40% in cases of BT [14, 15], and 0% to 17% in cases of NR without BT [11, 14, 15]. These numbers vary depending on the regimen, but overall, a longer duration of retreatment and a higher dosage of IFN produces a higher SR rate [10, 11, 14].

In most of these studies, the patients were treated with IFN-α; thus, the question remains about the efficacy of switching the type of IFN between the first and second treatments. In the present study, therefore, we analyzed data from patients treated with IFN-α (recombinant and native), IFN-β, and Natural human IFN-α Otsuka (OIF) to investigate the effectiveness of each IFN for retreatment. Furthermore, most previous studies do not report detailed criteria for categorizing patients based on the first treatment cycle. However, we consider this detailed analysis to be valuable since the prediction of efficacy of retreatment is essential to be able to judge the applicability of the treatment. In the present study, we assigned patients to one of 3 groups based on their response to the first treatment: IR (incomplete response), PR (partial response) or NR (no response); patients were also identified according to whether or not they suffered a breakthrough (Table 1).

Previous studies have shown that a therapy that combines IFN-α and ribavirin, an anti-viral agent, results in an improved response in both initial treatment and retreatment [16, 17]. Depending on the regimen, however, increased adverse effects from the combination therapy also increases the number of patients discontinuing therapy [16]. Furthermore, although combination therapy is the most effective in cases of HCV-1b hepatitis, IFN-α alone has been found to be superior in some cases [17]. Finally, the medical cost of combination therapy is significantly higher than that of IFN therapy alone. Thus, IFN therapy alone must be maintained as an option for patients with poor tolerance, patients with a particular genotype of HCV and patients for whom cost is an issue.

Methods

Patients. This retrospective cohort study included 145 patients who were admitted to our hospital from 1988 through 2000. All had a well-established diagnosis

Table 1 Assessment of response to treatment

Criteria		Definition	
Abbreviation	Nomenclature	HCV-RNA at 6 months after treatment	ALT at 6 months after treatment
SR	Sustained response	Negative	
IR	Incomplete response	Positive	Normalized
PR	Partial response	Positive	Less than double of upper limit of normal range.
NR	No response	Positive	No change in ALT level
BT	Breakthrough	Once cleared, but reappears during treatment	Once normalized, but relapses during treatment
ETR	End of treatment response	Cleared at the end of treatment	Normalized at the end of treatment

The response to the treatment is assessed by both serum HCV-RNA and serum ALT level at 6 months after treatment.

of chronic hepatitis C confirmed by liver biopsy and positive HCV antibody test. Prior to treatment, other liver diseases were excluded by appropriate medical history and physical and laboratory data including negative HBsAg and ceruloplasmin levels.

The baseline laboratory parameters were measured, including the mean serum ALT, albumin, alkaline phosphatase, and bilirubin levels, prothrombin time, and partial thromboplastin time. Serum levels of total bilirubin were < 2.0 mg/dl for all patients, and serum levels of albumin were > 3.0 g/dl. Clinically detectable ascites, edema, and encephalopathy were absent in all patients. All patients gave their written or oral informed consent prior to treatment.

IFN. Recombinant IFN-α2b was obtained from Schering-Plough, Inc. (Osaka, Japan), recombinant IFN-α2a was obtained from Hoffmann-La Roche, Inc. (Nutley, NJ, USA), IFN-α was obtained from Sumitomo Pharmaceuticals, Inc. (Osaka, Japan), IFN-β was obtained from Kanebo Ltd. (Tokyo, Japan), and IFN-OIF was obtained from Otsuka Pharmaceutical Factory, Inc. (Tokushima, Japan). In the present study, both recombinant IFN (α2a, α2b) and native IFN (α, β, OIF) were used (Table 2). IFN-α2a, IFN-α2b, IFN-α, and IFN-OIF were injected intramuscularly for 24 weeks, and IFN-β was administered by intravenous injection for 6 weeks.

Study design. All 145 patients, who had undergone liver biopsy, underwent a first treatment course with one of the IFN subtypes (α2a, α2b, α, OIF or β). During the first IFN cycle, which lasted 6 weeks to 6 months, the patients received either 3, 5, 6 or 10 MIU of the appropriate IFN 3 times per week. After 6 to 76 months of observation, a second IFN treatment was started at a higher dose or at the same dose of the same IFN to IR patients, or with a change to a different IFN for NR and PR patients; patients who achieved SR did not receive a second treatment (Fig. 1). During the second course of IFN treatment, the patients received either 3, 5, 6, 10 or 14 MIU IFN 3 times per week for 6 weeks to 6 months (Tables 2 and 3).

General laboratory tests. Laboratory tests were performed in the clinical laboratories of our medical

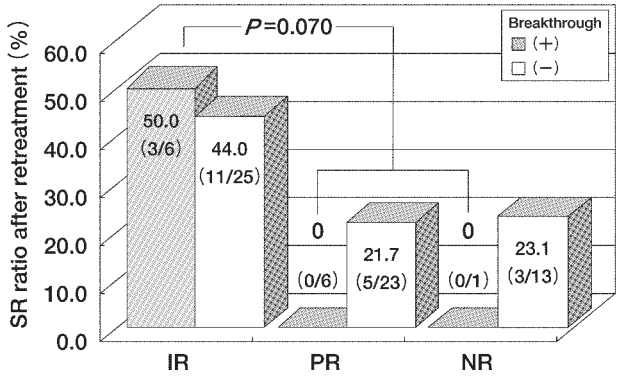

Fig. 1 Study design - description of cohort groups. A total of 145 patients were primarily treated with various types of IFN. The patients were assigned to one of 4 groups (SR, IR, PR or NR) depending on their response to the primary treatment. The cohort groups for the secondary treatment consisted only of the non-SR groups (IR, PR and NR). 16 non-SR patients did not receive a second treatment.

Table 2 Administration of IFN

IFN		Dose (MIU/week)	M/iv	Duration (weeks)
α2a	r	9	M	24
α2b	r	30	M	24
α	n	18	M	24
OIF	n	15	M	24
β	n	42	iv	6

The choice of IFN for treatment is shown. iv, intravenous injection; M, intra-muscular injection; n, native IFN; OIF, natural IFN-α provided Otsuka pharmaceuticals Co., Ltd., Tokyo, Japan; r, recombinant IFN.

Table 3 Regimen for IFN choice

Primary regimen	Secondary regimen
α2a (11)	α2a (1)
	α2b (8)
	α (2)
α2b (35)	α2a (3)
	α2b (28)
	α (4)
α (12)	α2b (10)
	α (2)
OIF (9)	α2a (2)
	α2b (4)
	α (2)
	β (1)
β (7)	α2b (4)
	α (1)
	OIF (2)

The combination of IFNs for the first and the second treatment is shown. The numbers in parentheses represent patients per group.

center using standard methods. Pre- and post-treatment liver biopsies were evaluated in a blinded fashion. The method of histopathological evaluation followed the classifications previously described [18].

HCV RNA. The baseline serum HCV RNA concentration for each patient was calculated as the mean of the HCV RNA concentrations during screening. Serum HCV RNA concentration was determined at weeks 8, 16, 24, 28, 38, 48 and 72 in the 24-week retreatment group and at weeks 4, 6, 10, 18, 30 and 54 in the 6-week retreatment group. Serum HCV RNA was determined by the quantitative multicycle reverse transcription-polymerase chain reaction (RT-PCR) method [19]. The assays were performed at an independent research institute by technicians who were blinded to the patients' treatment.

HCV genotypes. HCV genotypes and subtypes were identified by the PCR method described by Ohno [20]. Briefly, primers complementary to the conserved sequences of the 5' untranslated region of HCV genomes of the different genotypes were used in the RT-PCR reactions. HCV RNA was extracted from the patients' sera and amplified by RT-PCR for the first round of amplification. The samples were amplified again with another set of primers using the nested-PCR method. The amplified fragments from the second round of PCR were subcloned into TA cloning vector for sequencing. Genotyping of the viruses was then conducted according to the obtained sequences [20].

Assessment of response to treatment. The efficacy of the primary treatment was assessed at 6 months after treatment according to the criteria established by the Japanese Ministry of Health and Welfare and those described byYano [21] (Table 1). An HCV RNA responder was defined as a patient with 2 consecutive undetectable (<100 copies/ml) values. If HCV RNA remained negative for 6 months, the patient was assigned to the SR group and did not undergo a second treatment. If HCV RNA was positive, the patient was assigned to the IR or PR group, depending on whether his or her ALT was normalized or partially responsive, respectively. ALT response was defined as 2 consecutive normal ALT values ($\leqq 48$ U/L); ALT was measured at the end of the 24-week treatment period and again at the end of the 24-week post-treatment observation period. Partial ALT response was defined as a reduction of ALT level to less than double the upper limit of the normal range. If neither HCV RNA nor ALT showed any response, the patient was assigned to the NR group. If HCV RNA was negative at the end of the 6-week or 6-month treatment, the patient was defined as ETR (end of treatment response). If HCV RNA reappeared during treatment, the patient was defined as BT.

Anti-IFN antibody. Anti-IFN antibody was measured by biological neutralization assays (SRL, Hachioji, Japan). In brief, a series of IFN-antiserum mixtures were prepared containing varying dilutions of antiserum. The mixtures were incubated for 1 at 37 °C, and placed on the assay cells for observation of antiviral effect. The neutralization titer was measured by comparison to the control assay which did not include antiserum.

Statistical methods. Noncontinuous variables, such as analyses of efficacy of treatment and comparison of patients' background, were assessed by χ^2-test or Fisher's exact probability test. Statistical comparison between the SR and non-SR groups concerning the age of the patients, months from 1st treatment and ALT upon initiation of retreatment were assessed by Mann-Whitney U Test. $P<0.05$ was considered to be significant

Results

Demography of the study population. After primary treatment with IFN, 55 of 145 patients (37.9%) achieved SR. Of the 90 patients who were resistant to IFN (NR, IR and PR), 74 fulfilled the requirements for secondary treatment: 31 cases of IR, 43 cases of PR or NR. The overall rate of SR after secondary treatment with IFN was 29.7% (22/74) and that of non-SR was 70.3% (52/74, Table 4).

Side effects and tolerance to treatment. The side effects of IFN retreatment requiring reduction of therapy were fatigue and fever in 2 patients, headache in 2, depression in 1, psychological effects in 4, skin rash

Table 4 Efficacy of the primary treatment and the secondary treatment

Treatment	Total patient number	SR	IR	PR	NR
Primary	145	55 (37.9%)	36 (31)	33 (29)	21 (14)
Secondary	74	22 (29.7%)	17	24	11

Of primary treatment, 16 patients did not receive secondly treatment because of their disinclination. ( ), cases received second treatment.

in 1, anemia and leukopenia in 1, hypothyroidism in 1, elevated serum/urine amylase in 3, aggravation of diabetes mellitus in 2, interstitial pneumonitis in 1, and proteinuria in 1. Although retreatment was reduced in these cases, none of these patients ceased retreatment due to side effects of the IFN.

Predictors from the patients' background. Analysis of the patients' background showed no significant difference in age between those who achieved SR and those who were defined as non-SR with retreatment (Table 5). Likewise, the levels of ALT of these groups at the start of retreatment were not significantly different. We next analyzed the stages and grades of the SR and non-SR groups according to Desmet's classification of chronic hepatitis [22]. The occurrence of stage 0 and stage 1 (S0 and S1), or that of grade 0 and grade 1 (G0 and G1) was not significantly different between the SR and non-SR groups (Table 5). The number of patients with a low level of HCV RNA (< 100 Kcp/ml) was 5 of 22 (22.7%) in the SR group and 5 of 52 (9.6%) in the non-SR group and there was no statistical difference. The number of patients with a high total dose (> 400 MU) was also not significantly different. The ratio of patients whose response to the primary treatment was IR was significantly higher in the secondary SR group (14 of 22) than that of patients in the secondary non-SR group (17 of 52).

The choice of IFN did not produce any significant effect on the overall response to the secondary treatment: SR group (IFN-recombinant α/native $\alpha/\beta = 17/5/0$) *vs.* non-SR group (29/16/7). When the ratio of patients with HCV-1b was compared between the SR group and the non-SR group, there was a significantly higher number of such patients in the non-SR group: 10 of 22 (45.5%) in the SR group *vs.* 37 of 52 (71.5%) in the non-SR group (Table 5).

Anti-IFN antibody. The sera from 13 patients who were designated NR upon ETR were tested for IFN antibody. When analyzed after primary treatment, 1 patient of the 13 was positive for anti-IFN antibody. It is of note, however, that this patient also fell into the NR group after retreatment.

Efficacy of retreatment with IFN among non-SR patients. The efficacy of different combinations of IFN was compared (Table 6). In the primary IFN-α2a non-SR patients, efficacy was found to be 0% for retreatment with IFN-α2a and 30% (3/10) with a different IFN (α2b, α). In the primary IFN-α2b non-SR patients, efficacy was 50% (14/28) with IFN-α2b retreatment and 0% (0/7) with a different IFN (α2a, α). In the primary IFN-α non-SR patients, efficacy was 0% (0/2) with IFN-α and 20% (2/10) with a different IFN (α2b). In the primary IFN-β non-SR patients, efficacy was 0% (0/7) with a different IFN (α2b, α, OIF). And finally, in the primary OIF non-SR patients, efficacy was 33% (3/9) with a different IFN (α2a, α2b, α, β).

Efficacy was compared between patients who were treated with the same type of IFN for both the primary and the secondary treatments, and between patients who

Table 5 Background of patients for the secondary treatment

	Response to IFN	
	SR (N = 22)	non-SR (N = 52)
Age of patients (y/o) (M ± SD)	53.3 ± 7.0	59.0 ± 9.3
Low HCV-RNA cases (< 100 Kcp/ml)	5/22 (22.7%)	5/52 (9.6%)
Ratio of HCV subtype 1b	10/22 (45.5%)*	37/52 (71.2%)*
Initial NR	3/22 (13.6%)	11/52 (21.2%)
Initial PR	5/22 (22.7%)	24/52 (46.2%)
Initial IR	14/22 (63.6%)*	17/52 (32.7%)*
Total dose (> 400 MU)	20/22 (90.9%)	45/52 (86.5%)
Months from 1st treatment (M ± SD)	27.8 ± 24.7	37.8 ± 31.8
ALT at the start of re-treatment (M ± SD)	69.8 ± 52.3	58.2 ± 44.4
(S0+S1)/total	2/22 (9.1%)	5/52 (9.6%)
(G0+G1)/total	1/22 (4.5%)	2/52 (3.8%)

The background of patients is compared between SR group and Non-SR group.
S0 + S1, Staging 0 + Staging 1; G0 + G1, Grading 0 + Grading 1 [22]. *$P < 0.05$.

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Table 6 Efficacy of the secondary treatment

Re-treatment \ Primary treatment	IFN	α2a	α2b		α	β	OIF
	α2a	0/1	0/3		—	—	1/2 (50%)
	α2b	2/8 (25%)	14/28 (50%)	*	2/10 (20%)	0/4	0/4
	α	1/2 (50%)	0/4		0/2	0/1	1/2 (50%)
	β	—	—		—	—	1/1
	OIF	—	—		—	0/2	—

The numbers represent numbers of SR cases / numbers of patients. The numbers in parentheses are percentage. —, No data. $*P < 0.05$.

Table 7 Comparison of efficacy between identical IFN and switched IFN

Type of IFN for the secondary treatment	Total case	SR case	SR ratio	
Same IFN	31	14	45.2%	*
IFN Switched	43	8	18.6%	*

Comparison of efficacy between groups where identical IFN is used and where IFN types are switched. $*P < 0.05$.

received different IFN's in the 2 treatments ("switched"). The efficacy of the group with the same IFN was 45.2%, and that of the switched group was 18.6%, a statistically significant difference ($P < 0.05$) (Table 7). An analysis of patients who received the same IFN in both treatments showed that the efficacy of the secondary treatment was highest (50%) in those patients who received IFN-α2b for both treatments.

Comparative group analysis among IR, NR and PR patients. We also analyzed the efficacy of the secondary treatment by dividing the patients into IR, PR and NR groups, with subgroups based on whether they suffered a breakthrough during the primary treatment (Fig. 2). In the breakthrough group in particular, the IR patients showed a higher response ratio for the secondary treatment (50%, 3/6) than either PR or NR patients (0%, 0/7) although there was no statistical significance ($P = 0.070$). The overall efficacy of the secondary treatment was 23.1% (3/13) among patients who suffered a breakthrough and 31.1% (19/61) with those who did not.

Discussion

There is no doubt that IFN plays an important role in the treatment of chronic hepatitis C [23]. Recently,

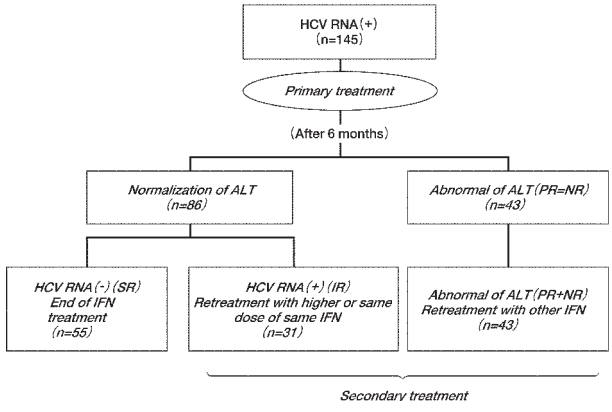

Fig. 2 SR ratio after the secondary treatment in breakthrough and non-breakthrough groups. Dark columns indicate breakthrough (+) groups. White columns indicate non-breakthrough (−) groups.

remarkable efforts have been made to improve the SR rate for initial treatment, and in the case of relapsers or non-responders, to successfully retreat them. There have been many attempts with successful results, such as combination therapy with the anti-viral reagent, ribavirin, and treatments involving a change of IFN administration to a higher dosage and/or a longer duration. A further approach is to switch the type of IFN in patients who did not respond to the primary treatment.

Prediction of IFN responsiveness based on the patient's background is beneficial in terms of choosing the most appropriate therapeutic approach. Previous reports have shown that the rate of response differs among HCV genotypes [12, 24]. These studies show that genotype 1b tends to be somewhat resistant to IFN-α. In the present retrospective study, the number of patients with HCV-1b was significantly higher in the non-SR group than in the SR group, indicating that the higher resistance of HCV-1b seems to remain in effect for the secondary

treatment.

Previous studies have indicated that a higher dosage and/or a longer duration of IFN therapy can improve the SR rate [25–27], although such treatments may entail negative consequences such as higher costs and a higher occurrence of adverse effects. Our data also suggest a positive correlation between a higher total dosage of IFN and the SR rate, but we have so far failed to detect any statistically significant effect of a higher total dose in improving outcome (Table 5). In order to confirm the beneficial effects of a higher total dose, either a larger patient group or a different analytical method may be necessary. For example, various IFN susceptibility factors of both host and viral contributions have been reported [4, 14]. With the advent of genetic analysis in clinical medicine, as yet unknown factors might be identified including viral gene variation for drug resistance or host genetic polymorphism by single nucleotide polymorphism analysis. If subcategorization of treatment depending on such factors becomes available, it may provide important and beneficial insight.

In a previous study, patients assigned to the NR group after primary treatment and retreated with the same type of IFN have shown an efficacy ranging from 0% to 17%, depending on the regimen [6]. The present study, using 6 weeks or 6 months of administration of the same type of IFN or a different type of IFN, shows a 45.2% and 18.6% SR rate, respectively (Table 7), which is statistically significant and furthermore, is considered to be a remarkable result. It is possible that the higher efficacy in the group treated with the same IFN may not necessarily be due to the superiority of the same-IFN protocol, but rather to the fact that this group represents the primary IR group, while the other group consists of NR and PR patients. This is compatible with the tendency of IR breakthrough patients to show a better response than NR or PR patients (Fig. 2, $P = 0.070$).

There are controversial arguments about the involvement of anti-IFN antibodies in non-responding or breakthrough cases. Some previous studies provide evidence suggesting that anti-IFN antibody is associated with the incidence of breakthrough [6–9]. On the other hand, there are also reports denying any correlation between the occurrence of anti-IFN antibody and breakthrough or failure to respond [15, 28, 29]. The discussion of the involvement of an anti-IFN antibody raises some technical questions about detection methods. If ELISA is used for the detection of anti-IFN antibody, 2 things must be taken into consideration. First, if IFN is immobilized onto the ELISA plate, the conjugation of IFN itself may sacrifice the epitope against anti-IFN antibody in the sample. Second, if sandwich ELISA is used, in cases where the 2 antibodies share the same portion of the epitope, this may also result in a masking of the epitope and consequently in a false negative result. To avoid these problems, we used a bioassay method to detect anti-IFN antibody. Our study shows that most of the non-responsive cases are not associated with anti-IFN antibody, although 1 patient of 13 cases did give a positive result for anti-IFN antibody. In fact, nearly half of the non-SR cases, as in many other reports [6–9], showed a good response to retreatment with the same IFN. Thus, anti-IFN antibody is not necessarily a major cause of non-responsiveness. It is worth bearing in mind, however, that the 1 patient who was positive for anti-IFN antibody after the primary treatment was assigned to the NR group after the retreatment.

In conclusion, our study suggests that retreatment with IFN alone is effective for some patients, especially when they are designated as IR after an observation period (Table 5). For such patients, retreatment with IFN-α2b is effective, especially when the primary treatment was also with IFN-α2b. We also suggest that in some cases it is effective to switch the type of IFN for non-SR patients since 18.6% of non-SR patients in the present study responded well to such a regimen. Additional studies with a greater number of cases are necessary, however, for statistical confirmation of this finding.

Acknowledgements. The authors would like to thank Professor Emeritus Takao Tsuji of the Department of Medicine and Medical Science, Okayama University Graduate School of Medicine, and President of Fukuyama National Hospital Shigeru Hirota for their valuable support and advice. We also thank Dr. Seizo Arita for his critical advice on the statistical analysis, Drs. Shingo Yasuhara, Kentaro Egusa, and Heidrun Fink for their critical advice and for reviewing the manuscript, Hiroshi Sinozawa of SRL for technical assistance, Satomi Saneto for her secretarial assistance, Kazuko Egusa, Yoko Nishiwaki, Junko Kawashima and Yoko Yasuhara for their devoted support, the paramedical staff at Fukuyama National Hospital for their excellent clinical assistance, and all the patients involved who agreed to participate in our work and supported it. This study was supported in part by a grant from the Ministry of Health and Welfare, 1980–2000.

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