
Original

Short-term interferon-beta treatment for
chronic hepatitis C with genotype 2 and low viral loads

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Abstract

Interferon (IFN) monotherapy leads to higher sustained virological responses (SVR) in patients with hepatitis C virus (HCV) genotype 2 and low viral loads. However, the optimal treatment duration is still in dispute. We evaluated the efficacy of short-term treatment with IFN- β (IFN- β) in patients with chronic HCV genotype 2 and low viral loads. This study included 25 patients with chronic hepatitis C with HCV genotype 2 and low viral loads who received 6 million units IFN- β intravenously daily for 8 weeks. All patients completed the 8-week treatment course. Serum HCV RNA disappeared from all patients within 4 weeks after the initial IFN-

β administration. The overall SVR rate was 84%. Ten of the 11 (91%), 10 of the 12 (83%) and 1 of 2 (50%) patients who exhibited serum HCV RNA disappearance 1 week, 2 weeks and 4 weeks after initial treatment achieved SVR, respectively. The ALT levels remained normal 24 weeks after the end of treatment in 19 of the 25 (76%) patients. Univariate analysis showed no predictive factors associated with SVR. There were no treatment discontinuations due to adverse events. Short-term treatment with IFN- β is an effective and well-tolerated treatment in patients with HCV genotype 2 and low viral loads.

Key words : chronic hepatitis C, interferon-beta monotherapy, genotype 2, low viral loads

I. Introduction

Approximately 170 million people worldwide are chronically infected with hepatitis C virus (HCV). HCV is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma^{1, 2)}. HCV clearance by interferon (IFN)-based treatment suppresses the progression of chronic liver disease^{3, 4)}. The efficacy of IFN-based treatment for chronic hepatitis C (CH-C) is predicted by factors such as HCV genotype, viral load before treatment

and early viral kinetics following treatment⁵⁻¹⁰⁾. In Japan, infection with HCV genotype 1 is predominant and HCV genotype 2 represents approximately 30% of all CH-C infections. Patients with chronic HCV genotype 2 are more sensitive to IFN treatment than those with HCV genotype 1^{5, 6, 8)}. Furthermore, patients with low viral loads are more sensitive to IFN treatment than those with high viral loads. Therefore, patients with chronic HCV genotype 2 and low viral loads show higher sensitivity

to IFN treatment. However, longer treatment duration tends to increase the frequency of adverse events. Therefore, it is necessary for us not only to achieve a high efficiency of treatment, but also to shorten the treatment duration. Moreover, although several studies have shown that treatment duration can be shortened in patients who achieve early serum HCV RNA disappearance after initial treatment¹¹⁻¹⁴⁾, appropriate treatment duration remains in dispute. We evaluated the efficacy of short-term treatment (8 weeks) with IFN- β (IFN- β) in patients with chronic HCV genotype 2 and low viral loads.

II. Patients and methods

1. Patients

Between 1997 and 2014, a total of 25 patients with chronic HCV genotype 2 infection and low viral loads ($<100\text{KIU/mL}$) were treated at Iwate Medical University Hospital and affiliated institutions with 8 weeks of IFN- β therapy. This was a retrospective cohort study. The enrollment criteria were as follows: i) age ≥ 16 years; ii) HCV RNA level $<100\text{KIU/mL}$ as determined by quantitative reverse-transcription polymerase chain reaction (RT-PCR); iii) genotype 2 (established using the method of Okamoto and colleagues¹⁵⁾); iv) chronic hepatitis diagnosis based on liver biopsy within 12 months before study entry (histology was assessed using the METAVIR scoring system^{2, 16)}; the stage of fibrosis was graded on a 5-point scale and histological activity was graded on a 4-point scale) or based on clinical features and laboratory findings; v) leukocyte and platelet counts of at least $3,000/\mu\text{L}$ and $100,000/\mu\text{L}$, respectively. Patients with the following were excluded: HCV genotype

other than 2, liver cirrhosis, decompensated liver disease, liver disease of other causes, hepatitis B viral infection, human immunodeficiency virus infection, psychiatric disease. All patients provided informed consent before treatment.

2. IFN therapy

The patients received daily intravenous injection of 6 million units of IFN- β (Feron, Daiichi-Sankyo Co., LD. Tokyo, Japan), 6 days a week, for 8 weeks. The total IFN- β dose was 288 million units.

3. Determination of serum HCV RNA and HCV genotype

Peripheral blood samples were obtained before treatment, at 1, 2 and 4 weeks after the first injection of IFN- β , and every 4 weeks thereafter up to 32 weeks. The sera were stored at -80°C until the analyses. Serum HCV RNA levels were measured by quantitative RT-PCR (Amplicor Monitor HCV v. 2.0; Roche Molecular Systems, Inc., Pleasanton, CA, USA). The detection limit of this assay was 5KIU/mL . When the HCV RNA level was below the detection limit, qualitative RT-PCR (Roche Molecular Systems) was performed. Both quantitative and qualitative RT-PCR were carried out according to the manufacturer's instructions. HCV genotypes were determined by PCR according to the method of Okamoto and colleagues¹⁵⁾.

4. Evaluation of the efficacy of IFN therapy

HCV disappearance or undetectable HCV was defined as a level below the detection limit by quantitative RT-PCR and negative in qualitative RT-PCR. Sustained virological response (SVR) was defined as undetectable HCV RNA 24 weeks after treatment completion. Non-sustained virological response (non-SVR) was defined as detectable HCV RNA at the end of treatment, or undetectable HCV RNA at the end of treatment

Table 1. Baseline characteristics of the patients

Subjects	N=25
Gender (male/female)	13/12
Age (years old)	51 \pm 14
Body mass index *	24.4 \pm 3.7
Aspartate transferase (IU/L) *	55 \pm 42
Alanine transferase (IU/L) *	73 \pm 58
White blood cell count (/mL) *	4690 \pm 1168
Red blood cell count ($\times 10^6$ /mL) *	435 \pm 36
Hemoglobin (g/dL) *	13.5 \pm 1.2
Platelet count ($\times 10^4$ /mL) *	17.9 \pm 5.3
Liver histology	
Activity	0-1 / 2-3 13/5
Fibrosis	0-1 / 2-3 15/3
HCV-RNA (KIU/mL) *	32 \pm 28
Previous IFN treatment (yes/no)	1/24

*Data are expressed as mean \pm SD

but detectable HCV RNA 24 weeks thereafter.

5. Statistical analyses

We used the SPSS software package (SPSS Statistics 17.0 for Windows, SPSS Inc., Chicago, IL, USA) for statistical analyses. Treatment outcomes were analyzed on an intention-to-treat basis. The Mann-Whitney U-test or Chi-square test was performed to compare clinical parameters between the groups. Univariate analysis was performed using logistic regression. All *P*-values <0.05 as determined by the 2-tailed test were considered statistically significant.

III. Results

1. Patient characteristics

Table 1 summarizes the clinical features of the 25 patients, 13 men and 12 women, at baseline. Mean age was 51 years (range: 16-74). Mean serum HCV RNA level before treatment was 32 KIU/mL (range: 5-98). Mean serum alanine aminotransferase (ALT) level at baseline was 73 IU/L (range: 16-241). Liver biopsy was not

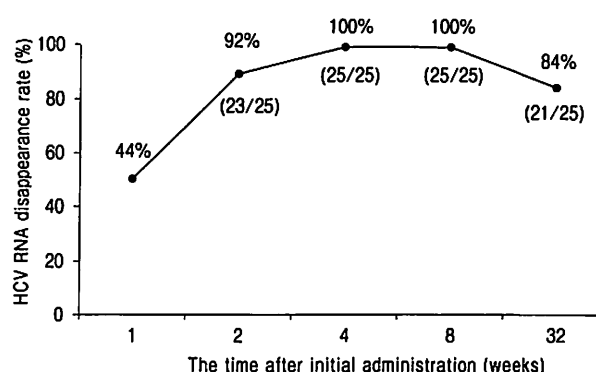


Fig. 1. HCV-RNA disappearance rate over time. Eleven of the 25 (44%) and 23 of the 25 (92%) patients were negative for serum HCV RNA at 1 week and 2 weeks after the initiation of IFN- β therapy, respectively. Serum HCV RNA disappeared from all patients within 4 weeks after the initial IFN- β administration. The overall SVR rate was 84%.

performed in 7 patients because of a bleeding disorder (1 patient) or refusal (6 patients). None had liver cirrhosis, based on clinical, laboratory, and histological findings. Twenty-four of the 25 patients received IFN treatment for the first time.

All patients completed the 8-week treatment course and were continuously followed up to 24 weeks after the end of the IFN therapy. Neither dose reduction nor discontinuation of IFN- β occurred during the treatment.

2. Responses to IFN- β treatment

HCV-RNA disappearance rates according to time are shown in Figure 1. Eleven (44%) and 23 (92%) of the 25 patients were negative for serum HCV RNA 1 week and 2 weeks after first IFN- β administration, respectively. Four weeks after the initial IFN- β administration, serum HCV RNA disappeared in all patients, and seronegativity persisted until the end of treatment. In 4 patients, HCV RNA reappeared within 24 weeks after the end of treatment. The

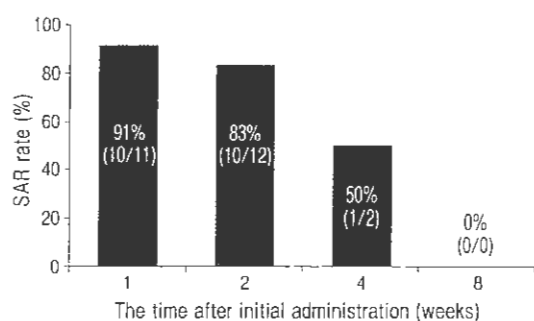


Fig. 2. Association between the timing of HCV-RNA disappearance and SVR

Ten of the 11 (91%) patients who exhibited serum HCV RNA disappearance 1 week after initial treatment achieved SVR. Ten of the 12 (83%) patients who had undetectable serum HCV RNA at 2 weeks achieved SVR.

overall SVR rate was 84% (21/25).

Figure 2 depicts the association between the timing of HCV-RNA disappearance and SVR. Of the 11 patients who were negative for serum HCV RNA 1 week after the initial IFN administration, 10 (91%) achieved SVR. Of 12 patients who were negative for serum HCV RNA 2 weeks after the initial treatment, 10 (83%) achieved SVR. Of 2 patients who were negative for serum HCV RNA 4 weeks after the initial treatment, 1 (50%) achieved SVR.

ALT levels remained within the normal range 24 weeks after the end of treatment in 17 of 21 (81%) patients who achieved SVR, but remained normal in only 2 of 4 (50%) who did not.

3. Predictors of SVR or non-SVR

Univariate analyses did not reveal predictive factors associated with SVR (including age, sex, body mass index, serum ALT, serum HCV RNA level, liver histology, white blood cell count, red blood cell count, hemoglobin and platelet count).

4. Safety

Adverse events are summarized in Table 2. The most frequent adverse events were influenza-like symptoms such as fever (≥ 38.5

Table 2. Adverse events

Adverse events	Number of cases (%)
Fever ($\geq 38.5^{\circ}\text{C}$)	22 (88%)
Headache	12 (48%)
Proteinuria	9 (36%)
Arthralgia / myalgia	6 (24%)
Fatigue	5 (20%)
Anorexia	3 (12%)

$^{\circ}\text{C}$) (88%) and headache (48%). Arthralgia or myalgia occurred in 6 patients (24%). These symptoms were well tolerated during treatment. Proteinuria appeared in 9 patients (36%). Neither leukopenia ($<2,000/\mu\text{l}$) nor thrombocytopenia ($<50,000/\mu\text{l}$) occurred. There were no treatment discontinuations due to adverse events and all adverse events were improved after IFN- β treatment. The IFN- β dose was not reduced in any of our patients during the treatment.

IV. Discussion

Patients with chronic HCV genotype 2 and low viral loads are sensitive to IFN treatment. In the USA and Europe, combination treatment with pegylated interferon (PEG-IFN) and ribavirin for 24 weeks is recommended for patients with HCV genotype 2 or 3, regardless of viral load^{17, 18)}. Previous studies on combination treatment for HCV genotype 2 or 3 have reported SVR rates ranging from 70% to 95%^{11-13, 19-22)}. However, long-term combination treatment increases adverse events induced by PEG-IFN or ribavirin. Several investigators have attempted to shorten the treatment duration to less than 24 weeks. The SVR rates with combination treatment in those studies with 12 to 16 weeks of treatment ranged from 59% to 94%^{19, 21, 22)}. In Japan, either IFN monotherapy or PEG-IFN monotherapy has been indicated as the

initial treatment for patients with HCV genotype 2 and low viral loads until 2014²³⁾. Although in our protocol the duration of IFN- β treatment was only 8 weeks, the overall SVR rate was high (84%). As to IFN- β monotherapy for less than 8 weeks, it has been reported that 60% of patients who received 6-week treatment achieved SVR²⁴⁾. In another report, 100% of patients who received 6-week treatment achieved SVR²⁵⁾. However, in this report, the number of patients was small and those patients were treated with IFN- α . Therefore, 8-week IFN- β treatment could be the optimal duration. In addition, in a group of patients who achieved HCV RNA disappearance at 1 week after initial treatment and received either 4 or 12 weeks of PEG-IFN monotherapy, the SVR rates for the 4-week treatment (91%) were approximately similar to those for the 12-week treatment (100%)¹⁴⁾. Response-guided therapy for patients with HCV genotype 2 and low viral loads might shorten the treatment duration and achieve higher SVR. In our study, approximately half of the patients achieved HCV RNA clearance from serum 1 week after the initial IFN- β administration, and 91% (10/11) of those patients obtained SVR. Thus, appropriately selected patients can expect shorter treatment durations and a higher SVR.

In this study, 4 patients relapsed during the treatment course. One patient refused re-treatment because of advanced age while 3 were re-treated. Two patients received 48 weeks of PEG-IFN treatment and one received 24 weeks of PEG-IFN plus ribavirin combination treatment, and all re-treated patients achieved SVR. We consider non-SVR patients who have received short-term treatment to have the potential to achieve SVR with re-treatment employing long-term PEG-IFN monotherapy or

PEG-IFN plus ribavirin combination treatment.

In 2015 in Japan, direct acting antivirals and ribavirin were indicated as the initial treatment for patients with HCV genotype 2²⁶⁾. These drugs will become mainstream for patients with HCV genotype 2. However, treatment with IFN- β may be available for patients infected with HCV genotype 2 and low viral loads who are unable to use an IFN-free regimen or who failed in an IFN-free regimen. In addition, the cost of IFN- β treatment is lower than that of an IFN-free regimen.

Also, because IFN- β has to be administered intravenously, daily administration may be cumbersome. However, there were no severe adverse events and no patients withdrew due to adverse events or laboratory abnormalities. Moreover, no IFN- β dose reductions were required in any of our patients during the treatment. Therefore, this 8-week IFN- β protocol is a safe and well-tolerated treatment for patients with chronic HCV genotype 2 and low viral loads.

In conclusion, we have shown that short-term treatment with IFN- β is an effective, well-tolerated and cheap treatment for patients with chronic HCV genotype 2 and low viral loads. A large scale study to further investigate the significance of short-term IFN- β treatment for chronic HCV genotype 2 with low viral loads is warranted.

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Conflict of interest: The authors have no conflict of interest to declare.

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Genotype 2 型低ウイルス量 C 型慢性肝炎に対する interferon-beta 短期治療

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要旨

Interferon (IFN) 単独療法により Genotype 2 型低ウイルス量の C 型肝炎ウイルス (hepatitis C virus: HCV) を有する患者は高率に sustained virological responses (SVR) が得られる。しかしながら、最適な治療期間については議論がある。今回、我々は Genotype 2 型低ウイルス量の C 型慢性肝炎に対し IFN-beta (IFN- β) の 8 週間短期治療を行い、その有効性を評価した。Genotype 2 型低ウイルス量の C 型慢性肝炎患者 25 例を対象として、IFN- β 600 万単位を 8 週間連日静注にて投与した。全患者が 8 週間の治療を完遂した。IFN- β 治療開始後 4 週以内に全患者の血

清 HCV RNA は陰性化した。全体の SVR 率は 84% であった。IFN- β 治療開始後 1 週目, 2 週目, 4 週目までに HCV-RNA が陰性化した例の SVR 率は各々 91% (10/11), 83% (10/12), 50% (1/2) であった。25 例中 19 例 (76%) が IFN- β 治療終了 24 週後に ALT 値が正常範囲内となった。単変量解析で SVR に寄与する因子は描出されなかった。有害事象により治療を中断した例はなかった。Genotype 2 型低ウイルス量の C 型慢性肝炎に対する IFN- β の 8 週間短期治療は有効性と忍容性が高い治療である。