Large Dose Natural Interferon Alpha Therapy for Patients with Chronic Hepatitis C

OHMIYA, Misako
Department of General Medicine, Kyushu University Hospital

HAYASHI, Jun
Department of General Medicine, Kyushu University Hospital

FURUSYO, Norihiro
Department of General Medicine, Kyushu University Hospital

UENO, Kumiko
Department of General Medicine, Kyushu University Hospital

他

https://doi.org/10.15017/7239399

出版情報：福岡醫學雜誌. 88 (12), pp.380-388, 1997-12-25. 福岡医学会
バージョン：
権利関係：

原　　著

Large Dose Natural Interferon Alpha Therapy for Patients with Chronic Hepatitis C

Misako OHMIYA, Jun HAYASHI, Norihiro FURUSYO, Kumiko UENO
Yasuhiro KISHIHARA, Shigeki NABESHIMA and Seizaburo KASHIWAGI

Department of General Medicine, Kyushu University Hospital, Fukuoka 812-82

Abstract To evaluate the efficacy of large dose interferon treatment for patients with chronic hepatitis C virus (HCV) infection, we studied 99 Japanese patients treated with either 6 million units (MU) or 9 MU natural interferon alpha. Serum samples were tested for HCV RNA by polymerase chain reaction (PCR). HCV RNA genotypes were determined by PCR with type-specific preimers, and the HCV RNA level was measured by competitive PCR. HCV RNA was detected in all patients, prior to the initiation of treatment. We examined interleukin-1 receptor antagonist (IL-1 Ra) by enzyme-linked immunosorbent assay. Forty-four patients were treated with 9 MU natural interferon alpha for 24 weeks (group A), and fifty-five patients were treated with 6 MU natural interferon alpha for 24 weeks (group B). There were no significant differences in HCV RNA levels, HCV RNA genotype or histological activity index (HAI) score between the two groups. Of the 94 patients who completed this treatment, nine (23.1%) in group A and 14 (25.5%) in group B sustained elimination of HCV RNA throughout a 6-month follow-up. There were no differences in the rate of complete response when comparing HCV RNA genotype, levels and HAI score and no significant differences in elevation of IL-1 Ra levels between the two groups. Five of group A patients refused further treatment because of severe side effects such as retinal hemorrhage, while no patient in group B had severe side effects. Thus, large dose natural interferon alpha treatment confers no additional benefit to the patient, compared with the current use of a lower dose.

Key words : chronic hepatitis C ; large dose of interferon ; HCV RNA level ; HCV RNA genotype ; HAI score.

Introduction

Chronic hepatitis C virus (HCV) infection which is endemic in Japan[6)7)] often progresses to liver cirrhosis or hepatocellular carcinoma, effective treatment is vital. Interferon is effective for patients with chronic HCV infection as it can reduce serum aminotransferase levels and hepatocellular necrosis, control disease activity[10)18)], and eliminate HCV RNA from the sera[2)5)8)12)].

There are numerous reports concerning the treatment of chronic hepatitis C with interferon. We reported the effectiveness of a 6 million units (MU) natural interferon alpha treatment regimen for patients with chronic hepatitis C[9)]. On this regimen HCV RNA elimination was sustained throughout a 6-month follow-up in only one-third of the patients (complete responders), HCV RNA was elimi-

nated from the sera of one-third of the patients by the end of treatment, but re-appeared within the 6-month follow-up (partial responders), and in the remaining one-third of the subjects, HCV RNA was not eliminated at any time during the observation period (nonresponders).

Attempts have been made to improve response rates using higher doses of recombinant interferon alpha-2 b[1)20)21)] and by prolonging the duration of therapy[19)], with promising but variable results. On the other hand, a large dose interferon was found to induce large amounts of circulating interleukin-1 receptor antagonist (IL-1 Ra)[22)]. To evaluate the efficacy of a large dose of natural interferon alpha, we compared the outcome of interferon treatment and predictive markers such as HCV RNA levels and genotypes among patients treated with either 6 MU or 9 MU natural interferon alpha. The influence of IL-1 Ra to interferon treatment was also examined.

Materials and Methods

Patients

The 99 Japanese patients with chronic HCV infection were treated with interferon at Kyushu University Hospital, Japan. No patients had a history of alcohol, drug abuse or homosexuality. All patients were positive for both antibody to HCV (anti-HCV) by second-generation assay and HCV RNA and were negative for hepatitis B surface antigen (HBsAg) and antibody to human immunodeficiency virus (anti-HIV). Prior to treatment, liver biopsy was done for all patients. For a semiquantitative evaluation of histological changes, we used a numerical scoring system for histological activity index (HAI)[16)] score. HCV RNA was detected in all patients during the 6-month period prior to start of treatment.

Patients were assigned to two treatment groups, using a sealed envelope approach. Group A, 44 patients (32 men and 12 women) were given 9 MU natural interferon alpha and group B, 55 (40 men and 15 women) were given 6 MU natural interferon alpha. Ages ranged from 29 to 67 yr. (mean 50.3±11.0 yr.) in group A, and from 25 to 70 yr. (mean 49.5± 11.9 yr.) in group B.

In group A, HCV RNA levels before treatment were under 10^5 copies/50 μl in 25 patients and above 10^6 copies/50 μl in 19 (mean ; $10^{5.5\pm0.9}$ copies/50 μl). The HCV RNA of genotype lb was present in 34 patients, genotype 2 a in seven, and genotype 2 b in three. In group B, HCV RNA levels before treatment were under 10^5 copies/50 μl in 21 patients and above 10^6 copies/50 μl in 34 (mean ; $10^{5.6\pm0.9}$ copies/50 μl). The HCV RNA of genotype lb was present in 43 patients, genotype 2 a in 10, and genotype 2 b in two. (Table 1) There was no significant difference between the two groups regarding age, serum HCV RNA level, or HCV RNA genotype, before start of the treatmant.

Table 1 Patient characteristics before treatment

Characteristics	Group A	Group B
Number of patients	44	55
Age	29-67	25-70
(mean±SD years)	(50.3±11.0)	(49.5±11.9)
Gender(Men/Women)	32/12	40/15
HCV RNA levels (copies/50 μl)		
$\leqq 10^5$	25	21
$10^5 <$	19	34
mean	$10^{5.5\pm0.9}$	$10^{5.6\pm0.9}$
HCV RNA genotype		
1 b	34	43
2 a	7	10
2 b	3	2
HAI score		
-6	13	12
7-15	27	35
16-22	4	8

HCV ; hepatitis C virus
HAI, histological activity index

Methods

All serum samples were separated and stored at −20°C until tested for HCV RNA, HCV RNA genotype and HCV RNA level. Anti-HCV (HCV EIA II, Abbott Laboratories, North Chicago, Illinois)[7] was examined using enzyme-linked immunosorbent assay (ELISA). HBsAg and anti-HIV were examined using commercial serological tests.

Treatment regimen

The patients were given intramuscular injections of natural interferon alpha (human lymphoblastoid interferon, HLBI, Sumiferon, Sumitomo Co., Tokyo, Japan). In group A, a dose of 9 MU was given daily for 4 weeks, with 9 MU given three times a week for the next 20 weeks (total dose 792 MU). In group B, a dose of 6 MU was given daily for 2 weeks, with 6 MU given three times a week for the next 22 weeks (total dose 480 MU).

HCV RNA by PCR

Serum HCV RNA was detected by two-stage PCR, using primers from the 5'-noncoding region of the HCV genome: [3] 5'-CTGTGAGGAACTACTGTCTT-3' (sense; nt 28-47) and 5'-AACACTACTCGGCTAGCAGT-3' (antisense; nt 229-248) in the first stage, and 5'-TTCACGCAGAAAGCGTCTAG-3' (sense; nt 46-65) and 5'-GTTGATCCAAGAAAGGACCC-3' (antisense; nt 171-190) in the second stage.

Genotype of HCV RNA by PCR

The HCV RNA genotype was determined by two-stage PCR, using universal and type specific primers from the putative C gene of the HCV genome, according to the methods of Okamoto et al[17]. The first stage of PCR was performed with primers consisting of 5'-TGCGCGCGAC (TA) AGGAAGACTTC-3' (nt 137 to 158 from the HC-J I isolate, antisense). The second stage of PCR was performed with a sense primer consisting of 5'-AGGAAGACTTCCGAGCGGTC-3' (nt 148 to 167 from the HC-JI) and a mixture of four type-specific antisense primers. Antisense primers specific for the four HCV types were 5'-TGCCTTGGGGATAGGCTGAC-3' (nt 185 to 204, typl la), 5' GAGCCATCCTGCCCACCCCA-3' (nt 272 to 291, type lb), 5'-CCAAGAGGGACGGGAACCTC-3' (nt 302 to 321, type 2 a) and 5'-ACCCTCGTTTCCGTACAGAG-3' (nt 251 to 270, type 2 b). They were deduced from regions of the putative C gene where the sequences were preserved only by a group of isolates, with minor variations. The expected sizes of the products by the second stage of PCR were 57 base pairs (bp) (type 1 a), 144 bp (type 1 b), 174 bp (type 2 a), and 123 bp (type 2 b), respectively.

Level by competitive PCR

HCV RNA levels were quantified by competitive RT-PCR assay using synthetic mutant HCV RNA restricted by EcoRI in the 5'-noncoding region. HCV RNA from patients was mixed in each tube with the diluted mutant HCV RNA (10^2-10^7 copies/50 μl) and competitive PCR with the 5'-noncoding region was carried out. The amplified products were then restricted by EcoRI and analyzed electrophoresis, with mutant HCV RNA demonstrated at 105 bp and 113 bp and HCV RNA from patients at 218 bp. Size of the PCR product from patients was compared with that of the diluted mutant HCV RNA[13].

IL-1 Ra by ELISA

This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for IL-1 Ra is coated on the microtiter plate provided in the kit. Standards with known amounts of IL-1 Ra and samples are pipetted into the wells and any IL-1 Ra present is bound by the immobilized antibody. After washing away any unbound sa-

mple protein, an enzyme-linked polyclonal specific for IL-1 Ra is added to the wells and allowed to bind the IL-1 Ra which was bound during the first incubation. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of IL-1 Ra bound in the initial step. The color development is stopped and intensity of the initial step. The color development is stopped and intensity of the color is measured. A curve is prepared, plotting the optical density versus the concentration of IL-1 Ra in the standard wells. By comparing the optical density of samples to this standard curve, the concentration of IL-1 Ra in the unknown samples can be determined.

Statistical analysis

χ^2 test and analysis of variance with repeated measure were used to determine statistical significance of the date.

Results

Of the 99 patients, 94 completed treatments and the remaining five refused further treatment because of severe side effects. Of 44 patients in group A, 39 (29 men and 10 women) completed the interferon treatment and the remaining five stopped the treatment because of side effects. On the other hand, all group B patients completed the treatment. Biochemical and virological responses to interferon were evaluated in 94 (39 in group A, 55 in group B) of the initial 99 patients.

In group A, 9 (23.1%) responded completely, 16 (41.0%) responded partially, and 14 (35.9%) showed no response. In group B, 14 (25.5%) responded completely, 19 (34.5%) responded partially, and 22 (40.0%) showed no response. There were no significamt differences between the two groups.

Among patients with HCV RNA levels under 10^5 copies/50 μl, eight (38.1%) of 21 patients in group A and 12 (57.1%) of 21 patients in group B were complete responders (Table 2). Among patients with HCV RNA levels above 10^6 copies/50 μl, one (5.6%) of 18 patients in group A and two (5.9%) of 34 patients in group B were complete responders. The frequency of complete responders was significantly higher in patients with an HCV RNA level under 10^5 copies/50 μl than in those with a level above 10^6 copies/50 μl in each group. However, there was no significant differences in the number of complete responders based on the dose of interferon.

In patients with genotype 1 b, four (12.9%) of 31 in group A and eight (18.6%) of 43 in group B were complete responders. In patients with genotype 2 a, four (66.7%) of six in group A and five (50.0%) of ten in group B were complete responders. Of four patients of genotype

Table 2 A comparison of clinical features among chronic hepatitis C patients treated with natural interferon alpha

Characteristics	Group A		Group B	
	Patients	CR(%)	Patients	CR(%)
HCV RNA levels (copies/50 μl)				
$\leqq 10^5$	21	8(38.1%)[a]	21	12(57.1%)[e]
$10^5 <$	18	1(5.6%)[b]	34	2(5.9%)[f]
HCV RNA genotype				
1 b	31	4(12.9%)[c]	43	8(18.6%)
2 a	6	4(66.7%)[d]	10	5(50.0%)
2 b	2	1(50.0%)	2	1(50.0%)
HAI score				
- 6	11	2(18.2%)	12	5(41.7%)
7-15	25	7(28.0%)	35	7(20.0%)
16-22	3	0	8	2(25.0%)
Total	39	9(23.1%)	55	14(25.5%)

HCV ; hepatitis C virus
HAI ; histological activity index
a vs. b, c vs. d ; $p<0.05$
e vs. f ; $p<0.001$

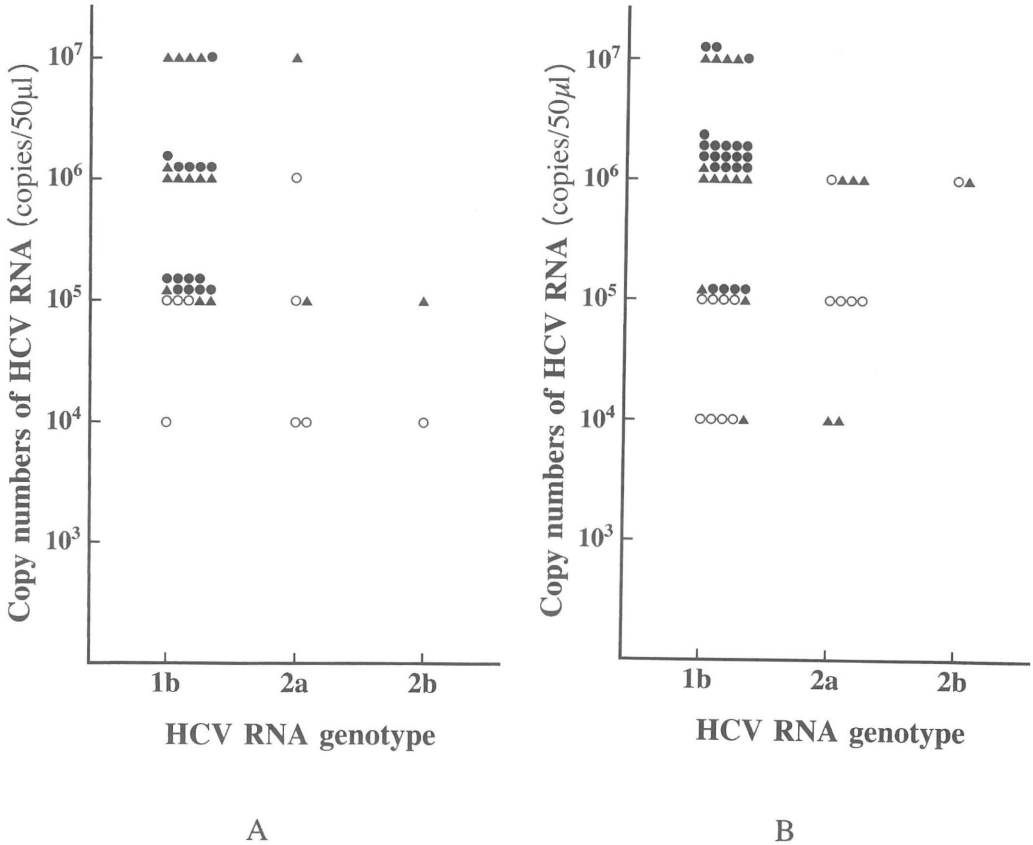

Figure 1. Correlation with hepatitis C virus RNA level and genotype.
(A)9 MU of natural interferon treatment.
(B)6 MU of natural interferon treatment.
○, complete responders ; ▲, partial responders ; ●, nonresponders.

2 b in group A and B, one (50.0%) of the two in each group was complete responder. The frequency of complete response was significantly higher in patients with genotype 2 a than in those with genotype 1 b, in each group. However there was no significant difference in the number of complete responders, based on the dose of interferon.

In patients with HAI scores under 6, two (18.2%) of 11 in groupA and five (41.7%) of 12 in group B were complete responders. In patients with HAI scores 7-15, seven (28.0%) of 25 in group A and seven (20.0%) of 35 in group B were ocomplete responders. In patients with HAI scores above 15, none of three in group A and two (25.0%) of eight in group B were complete responders. There was no significant difference comparing HAI score.

The relationship between HCV RNA genotype and HCV RNA level among patients after interferon treatment is shown Figure 1 A and 1 B. In patients with genotype 1 b with an HCV RNA level under 10^5 copies/50 μl, in group B, eight (53.3%) of 15 had a complete response while in group A, only four (28.6%) of 14 showed good effects. However, there was no significant difference between two groups. In patients with genotype 1 b with HCV RNA lev-

Table 3 Serum Soluble Interleukin-1 Receptor Antagonist

	sIL-1 Ra (units/ml, mean±SD)		
		After treatment	
Case(N)	Pretreatment	2 weeks	24 weeks
Group A 11	226.4±117.4	334.5±132.3	333.3±198.1
Group B 18	280.2±108.0	398.8±251.7	368.4±374.7

HCV ; hepatitis C virus
HAI, histological activity index

els above 10^6 copies/50 μl, complete responders were nil, in both group.

Normalization of ALT by the end of 24 weeks follow up was attained by 17 patients (43.6%) in group A and 23 patients (41.8%) in group B. There were no significant differences between the two groups when comparing HCV RNA levels, HCV RNA genotype and the HAI score.

We determined the level of IL-1 Ra by ELISA in 29 (11 in group A, 18 in group B) of 94 patients (Table 3). The ratio of IL-1 Ra at 2 weeks after the start of treatment to before the initiation of therapy was 1.9 in group A and 1.5 in group B. The ratio of IL-1 Ra at the end of therapy to prior to therapy was 2.0 in group A and 1.3 in group B. There was no statistically significant difference between group A and B.

Almost all patients had flu-like symptoms, including general fatigue and granulocytopenia. Side effects occurred in five (11.4%) in group A, including severe general malasise in one patients, severe headache in one, left leg paralysis in one, and severe granulocytopenia in two, and treatment was stopped. A 30 year old man in group A had slowly developing retinal hemorrhage while on interferon treatment.

Discussion

We expected that, to achieve a high rate of response, a large dose of interferon might be necessary for patients with genotype 1 b and a high level of HCV RNA which are unfavorable markers for interferon treatment[9]. However, our study shows that the rates of sustained elimination of HCV RNA and the normalization of ALT at the end of therapy and at 24 weeks follow up did not differ between large dose and regular dose groups. We investigated HCV RNA genotype, HCV RNA levels, and HAI score of liver tissue, but no differences between two groups were found. There are a few reports suggesting that either larger dose interferon or longer treatment might be necessary to prevent relapse.

It has been reported that a low HAI score, low HCV RNA levels and HCV RNA of genotype 2 a or 2 b were predictive markers of interferon treatment for patients with chronic hepatitis C[4)9)24)]. The present study revealed that these were also predictive markers of effectiveness with large dose interferon treatment. However, no differences between two groups were found. Tassoppulos et al.[21] suggested that a larger dose of interferon alpha does not improve the sustained response rate, but that it may be of benefit in the early stages of chronic hepatitis. In our study, the patients with low HAI score were less responsive to a large dose of interferon.

In some studies, patients were treated with the same total dose and different treatment regimens[11)23)]. Our treatment regimen was a different total dose. Iino et al.[11] suggested that the most effective treatment regimen was six days a week for two weeks by three times a week for an additional 12 weeks with 10 MU of interferon alpha-2 b. Further study to find

a more effective treatment for patients with chronic HCV infection is needed i.e ; combination treatments or long term treatment.

IL-1 is a mediator of inflammatory and growth processes and may play a role in chronic viral hepatitis caused by hepatitis B or hepatitis C viruses. We reported that the level of production of IL-1 was elevated in patients with chronic HCV infection and that the levels decreased in responders treated with interferon and elimination of HCV RNA[15]. Tilg et al.[22] found that interferon-induced IL-1 Ra was dose-dependent, larger doses of interferon alpha induced large amounts of circulating IL-1 Ra. In our patients, there were no significant differences in IL-1 Ra levels between the large and regular dose groups. We do not think that the low response rate was caused by an elevated IL-1 Ra.

Flu-like symptom, general malaise and pancytopenia commonly occurred in both groups ; however no 6 MU treated patient had to stop interferon therapy, indicating that the larger dose of interferon, although achieving similar results to the regular dose, is not as clinically beneficial, and severe side effects can occur in case of a large dose interferon treatment. Interferon retinopathy tends to develop in patients with diabetes mellitus or hypertension[14]. One of our patients in the large dose group had no retinal change and no such risk factors before start of interferon treatment but hemorrhage, occurred while on interferon treatment. Therefore, his retinopathy may be associated with a large dose of interferon.

By way of summary, a large dose of natural interferon alpha did not increase the rate of complete response and severe side effects led to discontinuation of the treatment.

References

1) Bellary S, Smith DG, Bankes P, Harris A, Shayiq R and Black M : High dose interferon alpha-2 b therapy for chronic hepatitis C : an open label study of the response and predictors of response. Am J Gastroenterol 90 : 259-262, 1995.

2) Chayama K, Saitho S, Arase Y, Ikeda K, Matsumoto T, Sakai Y, Kobayashi M, Unakami M, Morinaga T and Kumada H : Effect of interferon administration on serum hepatitis C virus RNA in patients with chronic hepatitis C. Hepatology 13 : 1040-1043, 1991.

3) Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW and Houghton M : Isolation of cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 244 : 359-362, 1989.

4) Hagiwara H, Hayashi M, Mita E, Takehara T, Kasahara A, Fusamoto H and Kamada T : Quantitative analysis of hepatitis C virus RNA in serum during interferon alpha therapy. Gastroenterology 104 : 877-883, 1993.

5) Hagiwara H, Hayashi N, Mita E, Ueda K, Takehara T, Kasahara A, Fusamoto H and Kamada T : Detection of hepatitis C virus interferon-alpha. Hepatology 15 : 37-41, 1992.

6) Hayashi J, Hirata M, Nakashima K, Noguchi A, Kashiwagi S, Matsui M, Ishibashi H and Maeda Y : Hepatitis C virus is a more likely cause of chronic liver disease in the Japanese population than hepatitis B virus. Fukuoka Acta Med 82 : 648-654, 1991.

7) Hayashi J, Nakashima K, Kishihara Y, Ohmiya M, Yoshimura E, Hirata M and Kashiwagi S : Improved detection of antibodies to hepatitis C virus by second-generation assay in patients with chronic non-A, non-B liver disease. J Infect. 26 : 287-294, 1993.

8) Hayashi J, Nakashima K, Noguchi A, Hirata M, Akazawa K and Kashiwagi S : Antiviral effect of interferon therapy for patients with chronic hepatitis C. Anti Chemi Chemo 3 : 305-309, 1992.

9) Hayashi J, Ohmiya M, Kishihara Y, Tani Y, Kinukawa N, Ikematsu H and Kashiwagi S : A statistical analysis of predictive factors of response to human lymphoblastoid interferon in patients with chronic hepatitis C. Am J Gastroenterol 89 : 2151-2156, 1994.

10) Hoofnagle JH, Mullen KD, Jones DM, Rustgi V, Dibisceglie A, Peter M, Waggoner J, Park Y and Jones EA : Treatment of chronic non-

A , non-B hepatitis with recombinant human alpha interferon. A preliminary report. N Engl J Med 315 : 1575-1578, 1986.

11) Iino S, Hino K, Kuroki T, Suzuki H and Yamamoto S : Treatment of chronic hepatitis C with high-dose interferon α-2 b, a multicenter study. Dig Dis Sci 38 : 612-618, 1993.

12) Kanai K, Iwasaki K, Nakao K, Kako M and Okamoto H : Suppression of hepatitis C virus RNA by interferon alpha. Lancet 336 : 245, 1990.

13) Kato N, Yokosuka O, Hosoda K, Ito Y, Ohto M and Omata M : Quantitation of hepatitis C virus competitive reverse transcriptation-polymerase chain reaction : Increase of the virus in advanced liver disease. Hepatology 18 : 16-20, 1993.

14) Kawano T, Shigehira M, Uto H, Nakama T, Kato J, Hayashi K, Maruyama T, Kuribayashi T, Chuman T, Futami T and Tsubouchi H : Retinal complication during interferon therapy for chronic hepatitis C. Am J Gastroenterol 91 : 309-313, 1996.

15) Kishihara Y, Hayashi J, Yoshimura E, Yamaji K, Nakashima K and Kashiwagi S : IL-1 β and TNF-α produced by peripheral blood mononuclear cells before and during interferon therapy in patients with chronic hapatitis C. Dig Dis Sci 41 : 315-321, 1996.

16) Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Thomas NK, Kiernan W and Wollman J : Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1 : 431-435, 1981.

17) Okamoto H, Sugiyama Y, Okada S, Akahane Y, Sugai Y, Tanaka T, Sato K, Tsuda F, Miyakawa Y and Mayumi M : Typing hepatitis C virus by polymerase chain reaction with typespecific primers : application to clinical surveys and tracing infectious sources. J Gen Virol 73 : 673-679, 1992.

18) Omata ZM, Ito Y, Yokosuka O, Imazeki F, Uchiumi K, Takano S, Hosoda K and Ohto M : Histological changes of the liver by treatment of chronic non-A, non-B hepatitis with recombinant leukocyte interferon alpha. Dig Dis Sci 34 : 330-337, 1989.

19) Reichard O, Foberg U, Frydén A, Mattsson L, Norkrans G, Sönnerborg A, Wejstål R, Yun Z-B and Weiland O : High sustained response rate and clearance of viremia in chronic hepatitis C after treatment with interferon-α 2 b for 60 weeks. Hepatology 19 : 280-285, 1994.

20) Sáez-Royuela F, Porres JC, Moreno A, Castillo I, Martines C, Galiana F and Carreño V : High doses of recombinant α-interferon or β-interferon for chronic hepatitis C : A randomized controlled trial. Hepatology 13 : 327-331, 1991.

21) Tassopoulos NC, Karvountzis G, Touloumi G, Delladetsima JK, Papatheodoridis GV, Katsoulodou A, Retails G and Hatzakis A : Comparative efficacy of a high or low dose of interferon α 2 b in chronic hepatitis C : A randomized controlled trial. Am J Gastroenterol 91 : 1734-1738, 1996.

22) Tilg H, Mier JW, Vogel W, Aulitzky WE, Wiedermann CJ, Vannier E, Huber C and Dinarello CA : Introduction of circulating IL-1 receptor antagonist by IFN treatment. J Immunol 150 : 4687-4692, 1993.

23) Toyoda H, Nakano S, Kumada T, Takeda I, Sugiyama K, Osada T and Kiriyama S : Effect of daily administration period of natural α-interferon in patients with chronic hepatitis C. Am J Gastroenterol 91 : 743-747, 1996.

24) Yoshioka K, Kakumu S, Wakita T, Ishikawa T, Itoh Y, Takayanagi M, Higashi Y, Shibata M and Morishima T. Detection of hepatitis C virus by polymerase chain reaction and response to interferon alpha therapy : relationship to genotypes of hepatitis C virus. Hepatology 16 : 293-299, 1992.

(Received for publication October 13, 1997)

(和文抄録)

C型慢性肝炎患者に対するインターフェロン大量投与

九州大学医学部総合診療部

大宮美佐香・林　純・古庄憲浩・上野久美子
岸原康浩・鍋島茂樹・柏木征三郎

(目的) C型慢性肝炎患者に対する天然型インターフェロン(nIFN) α の効果は，約30%とされており，特に高ウイルス量の例には効果が期待できない．著者らは，有効率を高めることを目的とし，IFNαの大量投与を行い，従来の投与量と，有用性について比較検討した．

(対象および方法) C型慢性肝炎患者99例に対してIFNαを投与した．IFNの投与は44例(グループA)に対して900万単位(MU)，毎日4週間，週3日20週間，計24週間，792 MU，55例(グループB)に対して600 MU，毎日2週間，週3日22週間，計24週間，480 MU投与した．hepatitis C virus RNA (HCV RNA)，その量，ゲノタイプはpolymerase chain reaction (PCR)法にて測定し，インターロイキン1受容体アンタゴニスト(IL-1 Ra)はenzyme-linked immunosorbent assay法にて測定した．IFN投与前，全症例ともHCVRNAは陽性であり，両グループ間には，HCVRNA量，ゲノタイプhistological activity index (HAI)スコアには差はなかった．IFN投与終了時および終了6ケ月にて，HCV RNAが陰性である症例を有効例とした．

(成績) グループAの5例は副作用により投与を中断したため，グループA39例，グループB55例，計94例について効果を検討した．有効率は，グループAで9例(23.1%)，グループBで14例(25.5%)であった．HCVRNAゲノタイプ，量，肝組織(HAIスコア)別に比較しても差はなかった．また，IL-1 Raのレベルも大量投与した症例と従来の投与量での症例とに差はなく，大量投与により高い効果が得られなかったのは，大量投与によりIL-1 Raが誘起されたことにはよらないと思われた．グループBでは全例投与終了したが，グループAの5例(11.4%)は，重篤な頭痛，全身倦怠感，下肢のしびれ感のため投与を中断し，別の1例は投与終了後，眼底出血をきたした．この症例は，投与前眼底検査には異常なく，糖尿病，高血圧など眼底出血をきたしうる基礎疾患を認めなかったため，大量のIFNによる変化と考えられた．副作用により投与中断した症例は，中断後すみやかに症状は軽快，消失した．

(結語) C型慢性肝炎患者に対するIFN大量投与は，従来の投与方法と有効率に差はなく，また重篤な副作用をもたらし，有用とは考えられなかった．