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Side effects of high-dose interferon therapy for chronic hepatitis C

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Background/Aims: **Various side effects have been reported in patients treated with alpha interferon, but their incidence and prognosis remain unknown.**

Methods: **Nine hundred and eighty-seven patients with chronic active hepatitis C received 6 to 10 MU of alpha interferon per day for 2 weeks and 3 times per week for 22 weeks. Autoantibodies, thyroid function tests, and fasting plasma glucose concentrations were evaluated prior to alpha interferon therapy.**

Results: **Of the 987 patients, 310 were required reduction in the dose of alpha interferon to 3 MU/day or cessation of alpha interferon therapy because of adverse reactions such as flu-like symptoms, leukopenia, and thrombocytopenia. Of the remaining 677, five developed diabetes mellitus, 12 had hyperthyroidism, and six acquired hypothyroidism. Of the 18 with thyroid disorders, five demonstrated antimicrosomal antibodies before therapy. Forty-four patients revealed high or low concentrations of thyroid stimulating hormone at the end of alpha interferon therapy. Three patients developed interstitial pneumonia, one acquired systemic lupus erythematosus-like syndrome, two had autoimmune hepatitis, two developed rheumatoid arthritis, and one developed autoimmune thrombocytopenic purpura. No patients had a history of an autoimmune disorder. One patient experienced sudden hearing impairment and one had retinal detachment. Melena was seen in three patients; two of these cases were compatible with ischemic colitis. Symptoms of depression were seen in 23 patients, and one patient manifested memory loss.**

Conclusion: **High-dose alpha interferon therapy induces various adverse effects. Most of the side effects cannot be predicted, but are reversible.**

Key words: **Chronic hepatitis C; Hearing impairment; Ischemic colitis; Retinal detachment; Side effects of alpha interferon.**

Alpha interferons (αIFNs) have been shown to be effective in non-A, non-B hepatitis (1–3). The Japanese Ministry of Healthcare has approved the use of IFNs for patients with chronic active hepatitis C (CAH-C) since January 1992. Since then, more than 160000 patients with CAH-C have received IFN therapy for the past 3 years in Japan and many side effects have been reported.

IFNs have a diverse biologic functions and act on many cells and organs. Although the severity of symptoms is directly related to the dose and frequency of administration, remarkable individual variation has been observed. Flu-like symptoms such as general malaise, fever, arthralgias and headaches, and the laboratory findings of leukopenia and thrombocytopenia are early adverse effects of high-dose αIFN administration. These adverse effects of IFN therapy could be defined as side actions of IFN, as opposed to side effects. The most popular IFN therapy protocol

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for CAH-C in Japan consists of 6 to 10 MU/day for 2 weeks, followed by 6 to 10 MU/day 3 times/week for 22 weeks. Because the average height and weight of patients in Japan are lower than Western patients, these doses of IFN for Japanese patients with chronic hepatitis C are higher than those used in Western countries.

High-dose or long-term IFN administration ultimately results in the appearance of various kinds of side effects (4–10), such as psychological disturbances, interstitial pneumonia, thyroid disorders, diabetes mellitus, retinopathy, autoimmune diseases, skin rash and loss of hair. It is important to evaluate the incidence of side effects of αIFN therapy for CAH-C.

In our 3-year experience of administering αIFN to 987 patients CAH-C, we observed various kinds of side effects, including melena and retinal detachment. In this paper, we describe the incidence and the nature of side effects induced by high-dose αIFN therapy.

Patients and Methods

From January 1992 to February 1995, 987 patients with CAH-C were treated with alpha interferon at the Third Department of Internal Medicine in the Kyoto Prefectural University of Medicine, the Department of Medicine in the Hoshigaoka-Kohseinenkin Hospital, the Department of Medicine in the Aiseikai-Yamashina Hospital and the Department of Medicine in the Yodogawa Christian Hospital. Three hundred and ten of the 987 patients with CAH-C required IFN dose reduction to 3 MU/day or interruption of IFN therapy because of adverse reactions such as flu-like symptoms, leukopenia and thrombocytopenia during therapy. Except for these 310 cases, 677 patients were analyzed in this study.

Of the 677 patients, 343 patients were treated with lymphoblastoid IFN (nIFN, Sumiferon; Sumitomo Pharmaceutical Company, Osaka, Japan, and OIF; Otsuka Pharmaceutical Company, Tokushima, Japan), 224 patients were treated with recombinant human IFN α 2b (rIFN α 2b, Intron A; Schering Plough Corporation, Kenilworth, NJ, USA) and 110 patients were treated with recombinant human IFN α 2a (rIFN α 2a, Roferon; Nippon Roche K. K., Tokyo, Japan). Four hundred and five patients were men and 272 were women. Their ages ranged from 19 to 70 years. The average ages were 45.1 years for men and 46.9 years for women. These patients first received IFN daily for 2 weeks while hospitalized and then approximately two-thirds of the patients were treated by their primary physicians. All patients, except for a few, were followed-up monthly as outpatients in the four participating hospitals.

All 677 patients demonstrated the presence of the anti-HCV antibody and the absence of HBsAg. Their liver biopsy histologic findings were all compatible with CAH. Prior to IFN therapy, all cases were tested for the presence of antinuclear antibody (ANA; negative, <1: 40 titer), anti-DNA antibody (negative <1:40 titer), thyroid-stimulating hormone (TSH; normal, 0.34-3.5 IU/ml), thyroxine (T4; normal, 4.5-13.0 μg/dl), tri-iodothyronine (T3; normal, 0.8-1.8 ng/ml), antithyroglobulin antibody (negative, <1:100 titer), antimicrosomal antibody (negative, <1:100 titer), and fasting plasma glucose (FPG). FPG, T3, T4 and TSH were checked after 2 and 4 months of therapy, and at the end of the treatment. Serum samples were obtained prior to the start of the therapy, after 2 weeks, 2 months and 4 months of therapy, and at the completion of IFN therapy.

The daily dose of nIFN α was 6 or 10 MU. The daily dose of rIFN α 2b and rIFN α 2a consisted of 6 to 10 MU and 6 to 9 MU, respectively. The protocol of this study called for a daily injection of IFN for 2 weeks and then 3 times weekly for 22 weeks.

All the patients in this study gave written informed consent to participate in these trials and all aspects of these studies were approved by the Ethical Committees of the four participating hospitals.

Results

Of the 677 patients, 92 patients (13.6%) tested positive for ANA, 105 (15.5%) tested positive for anti-DNA antibody, 8 (1.2%) tested positive for antithy-

TABLE 1

Change in the titer of autoantibodies during interferon therapy

Autoantibody	Titer before IFN therapy	Titer after IFN therapy
ANA	1: 40 (84)*	1: 40 (53)
		1: 80 (29)
		1: 160 (2)
	1: 80 (5)	1: 80 (2)
		1: 160 (1)
		1: 320 (1)
		1: 640 (1)
	1:160 (3)	1: 160 (1)
		1: 640 (1)
		1: 1280 (1)
Anti-DNA	1: 40 (104)	1: 40 (76)
		1: 80 (27)
		1: 160 (1)
	1: 80 (1)	1: 160 (1)

* No. of patients.

TABLE 2

Side effects of high-dose interferon therapy in 677 patients with chronic active hepatitis C

Side effect	No. of cases	Onset
Hyperthyroidism	12 (1.8%)*	12–24 weeks (16.8 weeks) **
Hypothyroidism	6 (0.9%)	12–24 weeks (17.7 weeks)
Diabetus mellitus	5 (0.7%)	6–24 weeks (14.3 weeks)
Interstitial pneumonia	3 (0.4%)	4, 5, 23 weeks
Autoimmune disorders	6 (0.9%)	5–20 weeks (14.7 weeks)
Intestinal bleeding	3 (0.4%)	12, 20, 24 weeks
Psychological disorders	24 (3.5%)	5 days–24 weeks
Cardiovascular disorders	5 (0.7%)	1–20 weeks
Eruption with itching	86 (12.7%)	3 days–12 weeks
Alopecia	205 (30.3%)	10–22 weeks
Retinopathy***	20–50%?	

* : Frequency of the side effect.

** : Average weeks of the onset.

***: The frequency reported by other Japanese doctors.

roglobulin antibody and 24 (3.5%) tested positive for antimicrosomal antibody before IFN therapy. Of the 92 patients positive for ANA, 53 (53/405; 13.1%) were men and 39 (39/272; 14.3%) were women. Of the 105 patients who tested positive for anti-DNA antibody, 63 (63/405; 15.6%) were men and 42 (42/272; 15.4%) were women. At the conclusion of IFN therapy, 36 (36/92; 39.1%) of the 92 patients showed an elevation of the titer of ANA. Twenty-nine patients (29/105; 27.6%) showed an elevation of the titer of anti-DNA antibody (Table 1). Of the eight patients with antithyroglobulin antibody, six showed an elevation of their titer upon completion of IFN therapy. Of the 24 patients who tested positive for antimicrosomal antibody, 22 patients developed an elevation of the titer of the antibody during or at conclusion of IFN therapy. Eleven patients had a FPG greater than 110 mg/dl, and among them six patients revealed a FPG over 140 mg/dl before therapy. The frequency of the side effects of IFN therapy observed in this study is shown in Table 2.

Endocrinological disorders

Of the 671 patients with an FPG of less than 140 mg/dl of FPG before entry into the study, five patients developed overt diabetes mellitus during IFN therapy. Of the five patients, one patient had been followed up

TABLE 3

Clinical features of 12 patients who developed hyperthyroidism during alpha interferon therapy

Patient no.	Age	Sex	IFN dose (MU/day)	Duration of therapy (weeks)	Thyroid autoantibody ATG	AMS	T3 (ng/ml)	T4 (μg/dl)	TSH (IU/ml)
1	33	F	rIFN α 2b 6MU	18	negative (negative)	negative* (1:1600)**	1.3 (3.4)	9.5 (16.9)	1.7* (0.03)**
2	35	F	nIFN α 6 MU	19	negative (negative)	negative (negative)	1.2 (3.5)	9.2 (17.6)	2.1 (0.02)
3	37	M	rIFN α 2b 10 MU	16	negative (negative)	negative (negative)	1.4 (3.1)	11.0 (19.8)	2.0 (0.03)
4	38	F	nIFN α 6 MU	12	negative (1:400)	1:400 (1:25600)	1.3 (10.5)	3.5 (4.4)	1.3 (0.02)
5	41	F	rIFN α 2a 9 MU	16	negative (negative)	negative (negative)	1.3 (2.7)	9.7 (19.9)	1.9 (0.04)
6	42	M	nIFN α 6 MU	12	negative (negative)	negative (negative)	1.1 (3.3)	6.9 (18.0)	1.9 (0.01)
7	44	M	nIFN α 6 MU	12	negative (negative)	negative (negative)	1.7 (4.6)	10.9 (19.9)	0.09 (0.01)
8	45	F	rIFN α 2b 10 MU	16	negative (negative)	negative (negative)	1.4 (3.9)	9.8 (17.2)	0.97 (0.03)
9	46	M	nIFN α 6 MU	24	negative (negative)	negative (negative)	1.6 (1.8)	10.7 (14.7)	2.5 (0.02)
10	52	F	nIFN α 6 MU	13	negative (negative)	negative (1:6400)	1.5 (6.5)	8.9 (25.0)	2.3 (0.01)
11	61	F	nIFN α 6 MU	20	negative (negative)	negative (negative)	1.1 (4.1)	7.3 (11.1)	1.9 (0.07)
12	64	F	rIFN α 2a 9 MU	24	negative (negative)	negative (negative)	1.6 (2.4)	12.9 (18.2)	1.6 (0.10)

* : Data at the start of interferon therapy.

**: Data at the onset of hyperthyroidism.

ATG: Antithyroglobulin antibody. AMS: Anti-microsomal antibody.

TABLE 4

Clinical features of six patients who developed hypothyroidism during alpha interferon therapy

Patient no.	Age	Sex	IFN dose (MU/day)	Duration of therapy (weeks)	Thyroid autoantibody ATG	AMS	T3 (ng/ml)	T4 (mg/dl)	TSH (IU/ml
1	46	F	nIFN α 6 MU	24	negative (negative)	1:400* (1:800)**	1.7 (1.0)	7.9 (3.7)	2.1* (146.0)**
2	49	M	nIFN α 6 MU	12	negative (negative)	negative (negative)	1.0 (0.2)	4.1 (1.8)	2.9 (78.0)
3	56	F	rIFN α 2b 6 MU	20	negative (negative)	1:800 (1:102400)	0.9 (0-5)	9.2 (1.4)	1.8 (63.7)
4	56	F	nIFN α 6 MU	12	negative (negative)	negative (negative)	1.6 (3.3)	8.1 (0.8)	3.5 (19.4)
5	62	F	nIFN α 6 MU	14	negative (negative)	1:1600 (1:6400)	3.1 (0.8)	1.0 (1.9)	1.7 (82.0)
6	67	M	nIFN α 6 MU	24	negative (negative)	1:800 (1:204800)	1.4 (1 0)	9.2 (2.4)	3.5 (87.4)

* : Data at the start of interferon therapy.
**: Data at the onset of hypothyroidism.
ATG: Antithyroglobulin antibody.
AMS: Antimicrosomal antibody.

by her primary physician after she was discharged. She developed mental status changes after 20 weeks of IFN therapy. Her plasma glucose level was 719 mg/dl on hospitalization and nonketotic hyperosmolar coma was diagnosed. Currently, her FPG has been well controlled by diet therapy only. Of these five patients, three continued to receive IFN therapy until the end of the protocol.

All five patients showed impaired glucose tolerance after their FPG levels recovered to pretreatment levels.

Thyroid disorders

Hyperthyroidism developed in 12 patients, as shown in Table 3. Eight patients were women and 4 patients were men. The onset of hyperthyroidism occurred after 12 to 24 weeks of therapy. Of the 12 patients, only one (Patient 4) had manifested antimicrosomal antibody titers (1:400) prior to IFN therapy; this rose to 1:25600 at 12 weeks of IFN therapy. Three patients began to manifest antimicrosomal antibody titers (1:1600, 1:400, 1:6400) at 18 and 13 weeks of IFN therapy, respectively. Seven patients discontinued IFN therapy when they were diagnosed with hyperthyroidism. Of the seven patients, five received propylthiouracil for 1 to 12 months and became euthyroid after treatment.

Hypothyroidism developed in six patients (Table 4). Four of the six patients tested positive for antimicrosomal antibody before therapy. The titer of antimicrosomal antibody in the four patients significantly increased when they developed hypothyroidism. Of the six patients, four discontinued IFN therapy and all six patients were treated with thyroxine for 4 to 18 months. Their thyroid function returned to normal. Of the 18 patients who developed thyroid disorders, 12 received nIFN α, four were treated with rIFN α 2b and two underwent rIFN α 2a therapy. No significant differences in the development of thyroid disorders among the patients who received these three kinds of IFN therapy were observed.

Except for the 18 patients who developed thyroid disorders, 32 patients showed low levels of TSH and 12 patients showed high levels of TSH at the end of IFN therapy, respectively. However, these 44 patients were asymptomatic.

Interstitial pneumonia

Three patients developed clinical and radiographic evidence of interstitial pneumonia during IFN therapy. All three patients were men and their ages were 46, 57 and 59 years. Of the three patients, one was treated with nIFN α and Chinese herbal medicine (Sho-Sai-Koto®), which has been frequently used for chronic hepatitis patients in Japan. However, the remaining two patients received IFN alone. The findings on chest roentgenogram, computed tomography of the chest and blood gas analysis were compatible with interstitial pneumonia. Interstitial pneumonia in these three patients resolved within 2 months of discontinuation of IFN.

Autoimmune disorders

One patient (a 58-year-old woman) received rIFN α 2b and 13 weeks later she developed a high fever, a skin rash and a dry cough. LE cell formation and

rheumatoid factor (RA test) became positive, suggesting a systemic lupus erythematosus (SLE)-like syndrome. The abnormal laboratory data returned to pretreatment levels approximately 6 months later.

Two patients (a 47-year-old woman and a 54-year-old man) developed autoimmune hepatitis with nIFN α therapy. In one patient, the ANA titer and γ-globulin increased from 1: 80 to 1: 640 and from 1.5 g/dl to 2.1 g/dl, respectively. Results of the patient's liver tests became significantly worse 20 weeks after the start of IFN therapy. After discontinuation of IFN therapy, the ANA titer, γ-globulin and alanine aminotransferase levels returned to pretreatment levels. The other patient developed autoimmune hepatitis 18 weeks after therapy and her clinical course was almost identical to the former patient.

Two patients (a 48-year-old woman and a 56-year-old man) developed symptoms and signs of rheumatoid arthritis at 12 weeks and 20 weeks after the onset of IFN therapy, respectively. The former patient received nIFN α for 2 weeks and three times weekly for 10 weeks, while the other patient was treated with rIFN α 2b for 2 weeks and thrice weekly for 18 weeks before the development of a rheumatoid arthritis-like condition.

One patient (a 54-year-old woman) receiving rIFN α 2a developed autoimmune thrombocytopenic purpura 5 weeks after starting IFN therapy. She reported subcutaneous and vaginal bleeding and her laboratory data on admission were as follows: WBC, 5800/μl; RBC, 397×10^4/μl; Hgb, 11.6 g/dl; Hct, 35.6%; Platelet count, 5000/μl; ESR, 115 mm/h; Prothrombin time, 100%; APTT, 33.4 s; ANA 1:40; Bleeding time, 12 min; Coagulation time, 10 min; PAIgG, 98.9 ng/10^7 cells; positivity for anti-platelet antibodies, and 19.6×10^4/μl nucleated cells and 180/μl megakaryocytes on examination of the bone marrow. IFN therapy was terminated and platelet transfusion and prednisolone therapy were instituted. She subsequently completely recovered.

Intestinal bleeding

Melena was observed in three patients during IFN therapy. Patient 1 (a 47-year-old woman) started IFN therapy with nIFN α and 1 month later she noticed melena without abdominal pain. Colonoscopy was performed on the same day and demonstrated hemorrhagic erosions from the rectum to the descending colon. She had been treated with indomethacin suppositories for prophylaxis of high fever and headache induced by IFN administration. No skin rash was present and her eosinophil count was 2.5% at the start of therapy. The blastoid transformation test (11) for indomethacin and nIFN α was negative. One week later, nIFN α and indomethacin were administered again, but no melena was noted. Patient 2 (a 55-year-old-woman) and patient 3 (a 65-year-old-man) developed the sudden onset of abdominal pain and melena after 23 weeks and 5 weeks of IFN therapy, respectively. Colonoscopy demonstrated edematous mucosa, erosions, scattered linear ulcers from the rectum to the descending colon in both patients. Biopsy specimens showed interstitial edema and hemorrhage associated with the infiltration of lymphocytes, plasma cells and eosinophils. All three patients stopped IFN therapy and their lesions were strikingly improved at the follow-up colonoscopy. Their platelet counts were 173000/μl, 87000/μl and 67000/μl on presentation with melena. Eosinophilia was not present in Patients 2 and 3.

Psychological disorders

Depression was diagnosed by psychologists in six patients during IFN therapy and another 17 patients showed symptoms of depression with IFN treatment. Four of the six patients were men and two were women. Their ages ranged from 35 to 64 years with a mean age of 54.4 years. All six patients discontinued IFN therapy. The onset of these symptoms and signs ranged from 5 days to 21 weeks after the initiation of IFN therapy. Two patients attempted suicide. However, all six patients recovered from their psychological disorders. One patient (a 58-year-old man) complained of memory loss after 20 weeks of IFN therapy and IFN therapy was discontinued. One month later he showed complete recovery.

Retinopathy

Patients with pre-existing hypertension, diabetes mellitus and ophthalmologic symptoms underwent ophthalmoscopy after 10 to 12 weeks of IFN therapy. Before IFN therapy, patients over 50 years old and the patients with diabetes mellitus or hypertension were examined by an ophthalmologist. Thus, we did not analyze the incidence of the development of retinopathy in 677 patients on IFN therapy.

A 40-year-old man, who received daily injections of nIFN α for 2 weeks and then 3 times weekly for 7 weeks, complained of visual disturbances. Ophthalmoscopy demonstrated leopard spots on the fundus, resulting in the diagnosis of retinal detachment induced by uveal effusion. He received methylprednisolone therapy without IFN administration, and 2 months later the uveal effusion resolved completely. Ophthalmoscopy before IFN therapy demonstrated no abnormalities of his retina.

Other side effects

A case of severe sensorineural hearing loss was noted in a 55-year-old woman who received daily injections of nIFN α for 2 weeks and then three times weekly for 14 weeks. Little improvement was seen in her audiogram 6 months later.

Skin rash with pruritus was noted in 86 patients (12.9%) and another 69 patients (10.3%) complained of pruritus without skin rash. Of the 86 patients, 12 received n IFN α, 46 were treated with rIFN α 2b, and 28 were on rIFN α 2a. rIFN α therapy was a significant ($p<0.001$) risk factor for the development of skin rash for the patients compared with nIFN α.

Although moderate proteinuria (less than 3 g/day) was frequently seen, nephrotic syndrome or renal failure did not develop in these patients.

Transient sinus tachycardia and ventricular premature beats were noted in five patients. IFN therapy was discontinued in one patient with ventricular premature beats.

Two hundred and five patients reported loss of hair. Most of the cases of alopecia were minimal or mild. No significant difference was noted in the development of hair loss among the three kinds of IFN therapy.

Discussion

We have described the incidence of side effects of αIFN in 677 Japanese patients with CAH-C who received 6 to 10 MU of αIFN daily for 2 weeks and then three times a week for 22 weeks. Thyroid disease was noted in 12 patients who developed hyperthyroidism and six with hypothyroidism. Only one of the 12 patients with hyperthyroidism had a positive test for thyroid autoantibody before therapy and none had a history of autoimmune disease. The onset of thyroid disease ranged from 12 to 24 weeks of therapy. However, thyroid dysfunction may have developed earlier as described by others (9). IFN administration leads to an increase in MHC class I antigen expression and may activate a clone of autoantibody-producing B lymphocytes. However, the mechanism of the development of thyroid disease with IFN is unclear. Some reports (4,7,12–15) have described a high incidence of the appearance of thyroid autoantibody and thyroid disease in patients treated with IFN. The prevalence of thyroid autoantibodies in hepatitis C patients and of the development of thyroid dysfunction in hepatitis C patients receiving IFN are variable (16). In the present study, except for the 18 patients with thyroid disease induced by IFN therapy, 32 patients had a low level of TSH and 12 had a high level of TSH at the end of IFN therapy. Schultz et al. (17) have reported the development of thyroid disease in two of 20 patients with chronic hepatitis C treated with αIFN. Gisslinger et al. (18) have reported that elevated TSH levels, without a change in T4 levels, have occasionally been noted in the patients treated with αIFN. We cannot exclude the progression to thyroid disease in the 44 patients with abnormal levels of TSH.

Of the 677 patients, five patients developed diabetes mellitus during IFN therapy. These five patients continued to have impaired glucose tolerance after their fasting plasma glucose recovered to baseline levels. Koivisto et al. (19) have reported that IFN stimulated counterregulatory hormone secretion and impaired glucose tolerance, insulin sensitivity and insulin clearance. They have speculated that insulin resistance induced by IFN could be due either to direct effects of IFN or indirectly to other immunomodulators or factors that were stimulated by IFN. However, of the four cases with pre-existing diabetes mellitus, the diabetes mellitus worsened with IFN treatment only in two patients. Fabris et al. (20) have reported a case of type 1 diabetes mellitus which developed during αIFN therapy for chronic hepatitis C. In our study, islet-cell antibodies were not examined and the exact mechanism underlying the development of diabetes mellitus induced by the administration of IFN remains unclear.

Interstitial pneumonia has been developed in 0.1 to 0.3% of patients with chronic hepatitis C receiving IFN in Japan. However, approximately two-thirds of these cases are associated with the use of Chinese herbal medicine, Sho-Sai-Koto, with IFN. IFN or Sho-Sai-Koto alone also induces interstitial pneumonia. However, combination therapy with IFN and Sho-Sai-Koto demonstrated an increase in the development of interstitial pneumonia (21). Sho-Sai-Koto contains seven kinds of extracted granules, including scutellariae radix, which has been implicated in the development of interstitial pneumonia (22). This combination therapy has subsequently been prohibited in Japan, resulting in a decrease in the development of interstitial pneumonia. However, the mechanism of the development of interstitial pneumonia is still unclear.

There have been reports of the exacerbation and development of autoimmune diseases (23–27) with IFN therapy. Other reports have shown a high frequency of autoantibody formation in the absence of clinically significant disease (18). Since IFN can act as an immunomodulator, IFN administration might induce autoimmune disorders such as systemic lupus erythematosus (28,29), rheumatoid arthritis (30), autoimmune thrombocytopenia (31,32) and autoim-

mune hemolytic anemia (33,34). We observed one patient with an SLE-like syndrome, two with autoimmune hepatitis, two with rheumatoid arthritis and one with thrombocytopenic purpura. Most of these patients did not have pre-existing autoimmune disease and the time of onset was variable.

αIFN exerts profound effects, such as inhibition of suppressor T cell function, augmentation of cytotoxic T-cell and natural killer cell function, activation of macrophage and monocyte secretion of cytokines, enhanced expression of major histocompatibility (MHC) class I and II antigens and others. Thus, the immunological actions could result in dysregulation between self-tolerance and activation of cells recognizing autologous antigens. However, it is very difficult to determine which mechanism is responsible for each side effect in individual cases.

Intestinal bleeding was noted in three patients, two of whom had thrombocytopenia. Colonoscopy demonstrated findings compatible with ischemic colitis in two patients and hemorrhagic erosions in one. The lesions were localized from the rectum to the descending colon. Drug allergy was not present in all three patients. Pecorai et al. (35) have reported a case of ulcerative colitis in a patient with leukemia receiving IFN therapy. However, ischemic colitis has not been previously reported as a complication of IFN. Sparano et al. (36) have documented the role of interleukin-2 and αIFN in the development of colonic ischemia. Therefore the development of ischemic colitis in IFN therapy must be considered.

Guyer et al. (37) and Seki et al. (38) have reported interferon-associated retinopathy. Seki et al. (38) and others demonstrated that interferon-associated retinopathy was seen in 20 to 50% of the Japanese patients with chronic hepatitis C receiving IFN. Retinopathy was noted approximately 8–10 weeks after the initiation of IFN therapy and spontaneously resolved during IFN therapy. However, careful observation is necessary for patients with diabetes mellitus and hypertension. Retinal detachment as a side effect of IFN had not yet been reported. The patient with retinal detachment associated with uveal effusion did not have evidence of hemorrhage from retinal blood vessels. The mechanism of the uveal effusion is unclear.

Depression, mania, hallucination, dementia and delirium are all serious side effects of IFN (39,40). These side effects have been observed more frequently in older patients (41) and the degree of nervous system toxicity was dose-related. In our study, six patients were diagnosed with depression, with two patients attempting suicide. The incidence of depression increased with the duration of treatment (39). This finding emphasizes the importance of careful monitoring of this side effect in IFN therapy for patients with chronic hepatitis C.

IFN frequently induced reversible sensorineural hearing loss (42). The present study also documented the development of severe hearing loss and the lack of significant improvement in the patient's audiograms 6 months after the cessation of IFN therapy. Although it is unclear whether this hearing loss was induced by IFN, careful monitoring for ototoxicity in IFN therapy is necessary.

We found a few patients with cardiovascular complications. However, effects were moderate and transient. Most of the patients who developed hypothyroidism and autoimmune disorders had pre-existing autoantibodies. However, the patients showing other side effects did not have correlation with a pre-existing autoantibody profile.

Recently it has been reported that 12 months of αIFN therapy can suppress the incidence of relapse after cessation of therapy in patients with chronic hepatitis C (43). The incidence of most adverse effects of IFN is usually dose- and duration-dependent. Careful attention should be paid to these patients when they receive long-term and high-dose IFN therapy. Many patients in this study required an adjustment in the daily amount of IFN because of side reactions or side effects during the 24-week protocol. Thus, it was very difficult to evaluate the relationship between the incidence of side effects of IFN and the dose of IFN administered.

In summary, high-dose and long-term IFN treatment for chronic hepatitis C patients induces various adverse effects involving many organs. Most of these effects are reversible when detected early. Therefore, careful observation is necessary for chronic hepatitis C patients during IFN therapy.

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