Latent thyroid dysfunction in patients with chronic hepatitis C virus infection and its relevance to emergence of symptoms after peg-interferon treatment

Kazuyoshi Ishikawa *1, Tohru Nitatori *1, Chihoko Nakakarumai *2,
Naoko Isobe *3, Yoko Kikuchi *1, Natsuko Zushi *4

Abstract

The present study investigated latent thyroid disorders in 36 patients (13 men; 23 women; ages ranging from 32 to 77 years; median, 62.5 years) with chronic hepatitis C who did not have extrahepatic complications and had not previously received interferon. The average ALT for the subjects was 60.8 IU/L (range: 8-188 IU/L). Low FT4 was seen in 5.6 %, and one patient clearly had high TSH and was diagnosed as having hypothyroidism. TSH abnormalities were seen in 22.2 %; most patients had high TSH and were women. TRAb and TG-Ab were detected in 16.7% each, microsome test in 9.1 %, and TPO-Ab in 5.9 %. High Tg was seen in 25.0 %. Among the entire subjects, the prevalence of positive thyroid autoantibodies or high Tg was 33.3%, which is higher than in the general population. Most patients with latent thyroid dysfunction had hypofunction and were women. A biological response modifier such as peginterferon for treatment of chronic hepatitis C may render a latent thyroid disorder overt. In fact we encountered two patients who developed hyperthyroidism during or after administration of peginterferon. These results suggest that periodic and careful thyroid function tests are required in patients with thyroid autoantibody prior to the start of interferon therapy. Any evidence of thyroid function exacerbation requires immediate cessation of interferon administration and appropriate counter-therapy.

Keywords：thyroidautoantibody, thyroid dysfunction, hepatitis C, peginterferon, thyroglobulin

Introduction

In Japan, interferon has been widely used as the antiviral agent for therapy of chronic hepatitis C and achieved some effect leading to the eradication of the virus accompanied with the improvement of clinical manifestations. However, interferon therapy was not necessarily effective against the patients with high viral load of genotype Ib infection, which accounts for about half of chronic hepatitis C cases in Japan. In 2005, peginterferon and ribavirin combination therapy was introduced for the treatment of high viral load of genotype Ib infection. In this therapy, the virus is eradicated in more than half the patients, thus markedly improving the sustained viral response rate (SVR) over the existing treatments. Due to the pharmacological properties of peginterferon, the drug is injected subcutaneously once a week as a general rule, and cold-like symptoms as adverse events are very mild and the quality of life (QOL) during the early treatment period has been clearly improved. However, the incidence of traditional adverse events, such as, the onset and exacerbation of autoimmune disease, depression, cytopenia, hair loss and fundal hemorrhage, has not decreased, and as a result, careful monitoring is recom-

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*1 Faculty of Nursing, Iwate Prefectural University
*2 Iwate Seiwa Hospital
*3 Health Administration Center, Iwate Medical University
*4 Chugai Pharmaceutical Company

mended in peginterferon therapy like before.

During peginterferon administration, effective drug concentrations in blood are maintained for a long period of time, and when combined with ribavirin, the antiviral action of peginterferon is enhanced. Hence, even more than conventional interferon therapy, it is necessary to pay attention to granulocytopenia, decrease of hemoglobin and the onset of autoimmune phenomena including common thyroid dysfunction which has been reported by many researchers[1]. However, the underlying detailed mechanisms of the onset of thyroid disorders have still remained uncertain. We encountered one patient who developed typical hypothyroidism immediately after the end of peginterferon and ribavirin combination therapy. In the present study, we investigated latent thyroid disorder in chronic hepatitis C and assessed the relationship between peginterferon therapy and latent thyroid disorder.

Materials and Methods

The subjects were 36 patients (13 men, 23 women; median age, 62.5 years; range, 32 to 77 years) with chronic hepatitis C who were treated in outpatient department, did not have extrahepatic complications, and had not previously received interferon. The average ALT was 60.8 IU/L (range: 8-188 IU/L) and the average HCV-RNA was 1964 KIU/mL (range: 5-5100). In addition, two more patients with chronic hepatitis C who had undergone peginterferon therapy were included as subjects. Additional two patients who developed hypothyroidism during or after treatment of peginterferon also were enrolled in this study for analysis of changes in ALT and thyroid autoantibodies levels.

Thyroid hormone and thyroid stimulating hormone

The blood levels of free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) were measured by electrochemiluminescence immunoassay (ECLIA).

Thyroid autoantibody

The blood level of TSH receptor antibody (TRAb) was measured by radioreceptor assay (RRA) and the blood levels of thyroid stimulating antibody (TSAb) and thyroid stimulation blocking antibody (TSBAb) were measured by bioassay radioimmunoassay (RIA). The blood level of anti-thyroglobulin antibody (Tg-Ab) was measured by enzyme immunoassay (EIA) or by a thyroid test according to the particle agglutination (PA) method. The blood level of anti thyroid peroxidase antibody (TPO-Ab) was measured using EIA or a PA-based microsome test.

Thyroglobulin

The blood level of thyroglobulin (Tg) was measured by ECLIA.

2'-5' oligoadenylate synthetase

The blood level of 2'-5' oligoadenylate synthetase (2-5 AS) was measured by the RIA double antibody method.

HCV core antibody

The level of anti-HCV core antibody (anti-HCV core) was measured by EIA.

Ethical considerations

The present study conformed to the guidelines of epidemiological studies devised by the Ministry of Health, Labor and Welfare, Japan, to prevent leakage of personal information, and were conducted for the purposes of social benefit.

Results

I. Thyroid hormone, thyroid autoantibody and thyroglobulin (Table 1)

1) FT3, FT4 and TSH levels in chronic hepatitis C

FT3 abnormalities were not seen in any

Table 1. Backgrounds of patients with HCV infection having no history of any interferon treatment.

	patient	age	sex	ALT	HCV-RNA	FT3	FT4	TSH	TRAb	Thy.T	TgAb	Tg	Micro.T	TPOAb
unit				(IU/L)	KIU/mL	pg/mL	ng/dL	μIU/mL	IU/L	index	U/mL	ng/mL	index	U/mL
normal range				40>		2.2-4.1	0.88-1.81	0.3-3.9	1.0>	100>	0.3>	30>	100>	0.3>
	1	73	M	77	190	2.6	0.88	2.5	1.0>			14.5		0.3>
	2	50	F	96	230	2.9	0.68	51.7	6.3			27.2		0.3>
	3	65	F	50	1300	2.9	1.22	4.6	1.0>	100>		32.0	100>	0.3>
	4	41	F	43	4300	3.1	1.12	0.7	1.0>	100>		11.8	100>	0.3>
	5	68	F	176	1500	2.9	0.93	1.6	1.0>			14.2	100	
	6	59	M	42	5100	3.4	1.05	1.0	1.3	100>		16.2	100>	
	7	71	F	44	1100	2.5	1.20	4.6	1.1	100>		35.1	100>	
	8	59	F	31	220	2.9	1.07	1	1.0>	100>		30.2	100>	
	9	74	F	62	1300	2.3	1.04	3.6	1.0	100>		68.1	100>	
	10	68	F	25	5000	2.7	0.85	7.9	1.0>	100>		25.8	100>	
	11	48	M	18	5	3.4	1.16	0.5	1.0>	100>		14.5	100>	
	12	63	F	95	2200	3.4	1.13	3.4	1.0>	100>		22.8	100>	
	13	44	F	29	4600	3.3	1.21	0.7	1.0>			28.8	100>	
	14	72	F	106	5100	3.1	1.34	0.8	1.0>	100>		16.9	100>	
	15	54	M	111	110	3.2	1.15	4.1	1.0>	100>		14.4	100>	
	16	77	M	39	1700	2.9	0.97	1.6	1.0>	100>		24.6	100>	
	17	76	F	60	2200	3.5	1.16	2.0	1.0	100>			100>	
	18	72	F	62	1900	3.2	1.16	2.1	1.1	100>			100>	
	19	76	F	51	2400	3.1	0.95	8.1	1.0>	100>			100>	
	20	74	F	27	4300	3.2	1.02	2.7	1.0>	100>			102,400	
	21	41	M	99	2800	3.4	1.7	0.3>	1.0>	100>	0.3>		100>	0.3>
	22	63	F	19	630	3.0	1.3	1.1	1.0>	100>			100>	0.3>
	23	32	F	13	4300	3.2	1.3	1.4	1.0>	100>			100>	0.3>
	24	45	F	8	5	3.1	1.2	1.1	1.0>	100>	1.6		100>	0.3>
	25	61	F	22	5	3.3	1.4	1.1	1.0>	100>			100>	
	26	49	M	124	910	3.3	1.3	0.9	1.0>	100>			100>	0.3>
	27	53	M	69	3700	3.5	1.5	3.4	1.0>	100>			100>	
	28	63	F	35	5	3.8	1.4	0.9	1.0>	100>			400	14.8
	29	62	F	31	2600	3.1	1.4	1.4	1.0>	100>			100>	0.3>
	30	45	M	118	1600	3.1	1.2	0.8	1.0>	100>	0.3>		100>	0.3>
	31	64	F	188	290	2.9	1.07	7.0	1.0>	100>			100>	0.3>
	32	54	M	76	5000	3.2	1.1	1.8	1.0>	100>			100>	0.3>
	33	41	F	57	1600	108	6.1	2.1	1.0>	100>			100>	
	34	76	M	13	200	3.2	1.1	2.3	1.0>	100>	0.3>		100>	0.3>
	35	63	M	30	1700	2.7	1.1	3.3	1.0>		0.3>			0.3>
	36	56	M	43	610	3.0	1.1	1.5	1.0>	100>	0.3>		100>	0.3>

Figures on a netted backgrouond indicate an abnormal value.

patient. Low FT4 was seen in two patients (5.6%); in one of these TSH was clearly elevated at 51.8 μIU/mL and the patient was diagnosed as having hypothyroidism, while in the other TSH was normal. Among the total subjects, TSH abnormalities were seen in eight patients (22.2%), and including the above-mentioned patient, TSH was abnormally high in seven patients including one man and six women. The patient with low TSH was a male. FT4 was normal in all subjects, except for the above-mentioned patient.

2) Frequencies of the thyroid autoantibodies

TRAb was detected in six patients (16.7%), five of whom were women. A thyroid test was conducted on 31 patients, but none of the patients tested positive. Tg-Ab was detected in one of six patients (16.7%) who were tested, and this patient tested negative to the thyroid test. A microsome test was conducted on 33 patients, and three patients (9.1%) tested positive, all women. One of these three patients exhibited a strong positive reaction, at 102,400-fold over the normal level. TPO-Ab was detected in one of 17 patients (5.9%) tested, and this patient had a mildly elevated microsome level, at 400-fold over the normal level.

3) Thyroglobulin

The level of Tg was high in four (25.0%) of the 16 patients tested. Three of these four patients had high TSH or mild TRAb.

4) Frequency of positive thyroid autoantibody and high thyroglobulin

Among the total patients, in 12 patients

(33.3%) either thyroid autoantibody was positive or thyroglobulin was high.

Ⅱ. Changes in thyroid hormone and autoantibody levels in peginterferon therapy

1) Case 1. Overt hypothyroidism (Figures 1a-1e)

Case 1 was a 57-year-old man with chronic hepatitis C and diabetes. In 1961, he had a lower leg fracture and received a transfusion. His serogroup was 2 and HCV-RNA titer was 710 KIU/mL. In this patient with a high viral load of serogroup 2, 60-80 μg of peginterferon (Pegintron ®) was administered subcutaneously once a week and 600-400 mg of ribavirin (Rebetol ®) was administered orally everyday over a 24-week period from July to December 2006. Aside from mild malaise and mild fever, the therapy was completed without any major adverse reaction. No major change was seen in peripheral blood findings. HCV-RNA dropped to below 5 KIU/mL at four weeks after the start of therapy, and was undetectable eight weeks after the start of therapy and has remained undetected since then. At six months after the end of therapy, HCV-RNA was undetectable, and anti-HCV core antibody gradually decreased (sustained virological response: SVR), thus suggesting that the patient had, for all intents and purposes, been cured of chronic hepatitis C infection. During peginterferon therapy, 2-5 AS activities remained high. ALT was mildly abnormal at the start of peginterferon therapy, but then remained normal from four weeks after the start of therapy to one month after the end of therapy.

Examination of the thyroid hormone dynamics revealed that at the end of therapy, FT3 and FT4 were mildly elevated and TSH was low. Subsequently, the patient was carefully monitored for latent hyperthyroidism, but at two months after the end of therapy, FT3 and FT4 decreased while TSH clearly increased, thus suggesting latent hypothyroidism. Furthermore, at that point, ALT began to increase again, and continued to increase to 165 IU/L at three months after the end of therapy. At that point, no notable clinical symptoms were evident, but the patient tested positive for microsomes test, TPO-Ab and TSBAb. The patient continued to be monitored, and one week later developed facial and neck edema, also known as non-pitting edemas, thus indicating overt hypothyroidism. Daily administration of 100 mg/day of levothyroxine sodium (Thyradin-S ®) quickly eliminated the edemas, and at four months after the end of therapy, FT3 and FT4 normalized and ALT also improved. TSH gradually decreased, but not below 10 μU/mL. At two to seven months after the end of therapy, the antibody titer for TPO-Ab and TSBAb also gradually decreased after levothyroxine sodium administration. Furthermore, Tg-Ab which the measurement was started from five months after the end of therapy showed a similar tendency.

2) Case 2. Latent hypothyroidism (Figures 2a-2d)

Case 2 was a 54-year-old man with chronic hepatitis C. His past medical history did not reveal any relevant information. The serogroup could not be identified and his HCV-RNA titer was 260 KIU/mL. In this patient with high viral load of non serogroup 1, 180 μg of peginterferon (Pegasys ®) was administered subcutaneously once a week for 48 weeks starting in April 2006. After the start of therapy, the patient did not experience adverse events, except for mild malaise and fever, and no marked changes were seen in peripheral blood findings. At eight weeks after the start of therapy, HCV-RNA dropped below 5 KIU/mL and was undetected 12 weeks after the start of therapy and remained undetected up to 28 weeks after the start of therapy. At 28 weeks after the start of therapy, the patient noticed a visual field defect and was diagnosed as having retinal detachment by an ophthalmologist. While its relationship to peginterferon was not clear, the therapy was discontinued at 29 weeks after the start of therapy. HCV-RNA was undetected at six

months after the end of therapy, and anti-HCV core antibody gradually decreased, thus achieving a sustained viral response (SVR). The above findings suggested that the patient had, for all intents and purposes, been cured of chronic hepatitis C infection. During peginterferon administration, 2-5 AS activities remained high. ALT quickly normalized after the start of peginterferon administration.

Examination of the thyroid hormone dynamics revealed that TSH was slightly high prior to the start of peginterferon therapy, but rapidly decreased after the start of therapy and dropped below the normal range at 24 weeks after the start of administration. It remained low until two months after the end of administration, when the level then clearly increased to 10 μU/mL and then rapidly decreased to within the normal range. FT3 and FT4 were normal after the start of peginterferon therapy, and at 28 weeks after the start of administration, only FT3 mildly increased temporarily with a mild increase in ALT. During the entire course of therapy, no clear symptoms indicative of thyroid dysfunction were seen. At five months after the end of therapy, thyroid autoantibodies were tested: microsome test exhibited a 400-fold increase over normal levels, TPO-Ab was mildly elevated at 4.9 U/mL, and TRAb was undetected.

Discussion

Interferon therapy for chronic hepatitis C has been performed widely since first being covered by the national health insurance system in 1992. Initially natural α and β interferon and recombinant α interferon were used. At that time, interferon was adminis-

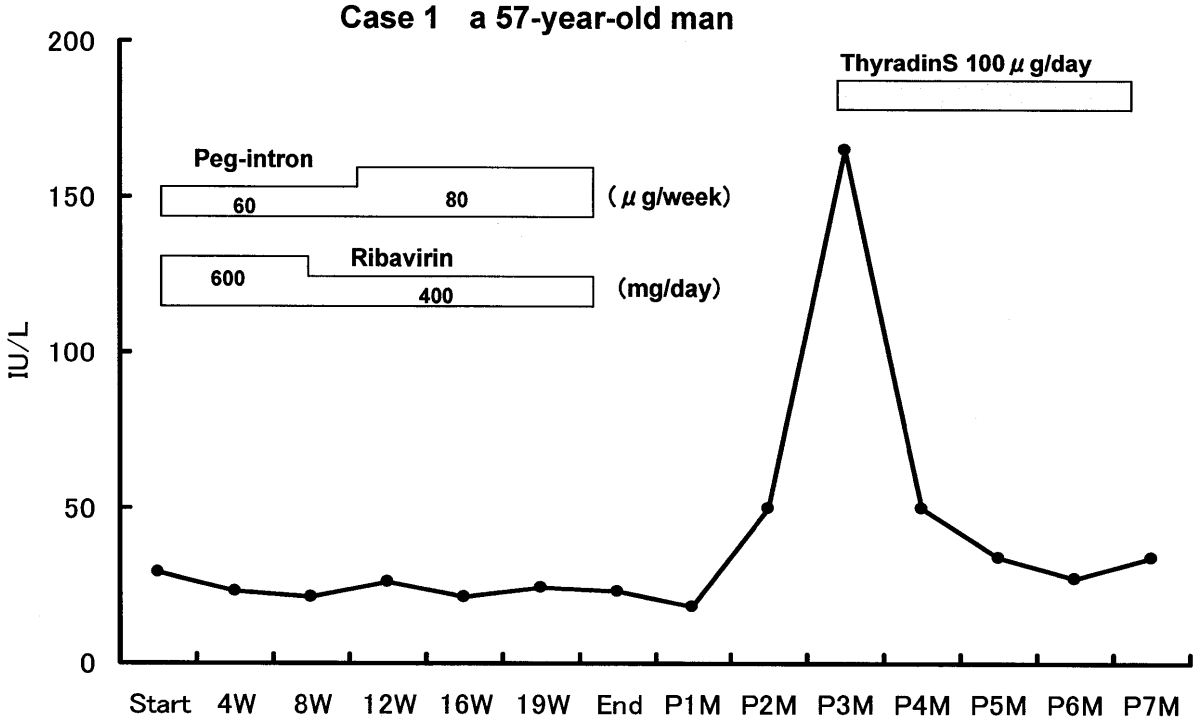

Figure 1-a. Changes of ALT value

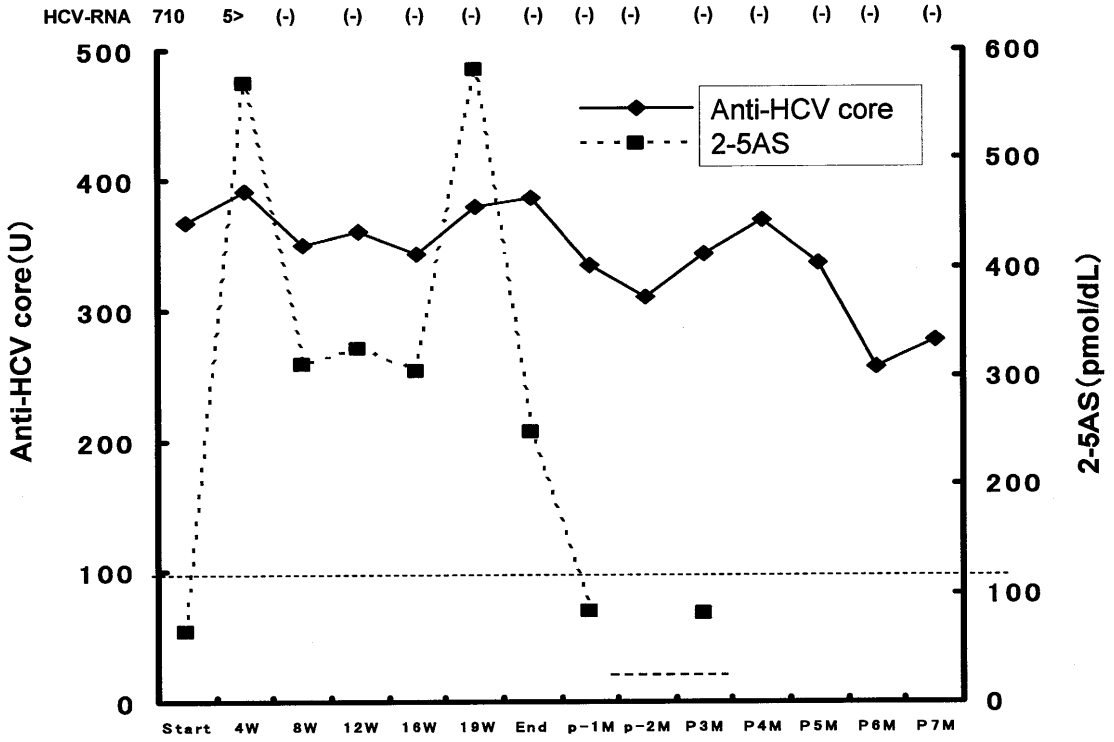

Figure 1-b. Changes of anti-HCV core and 2-5AS activity

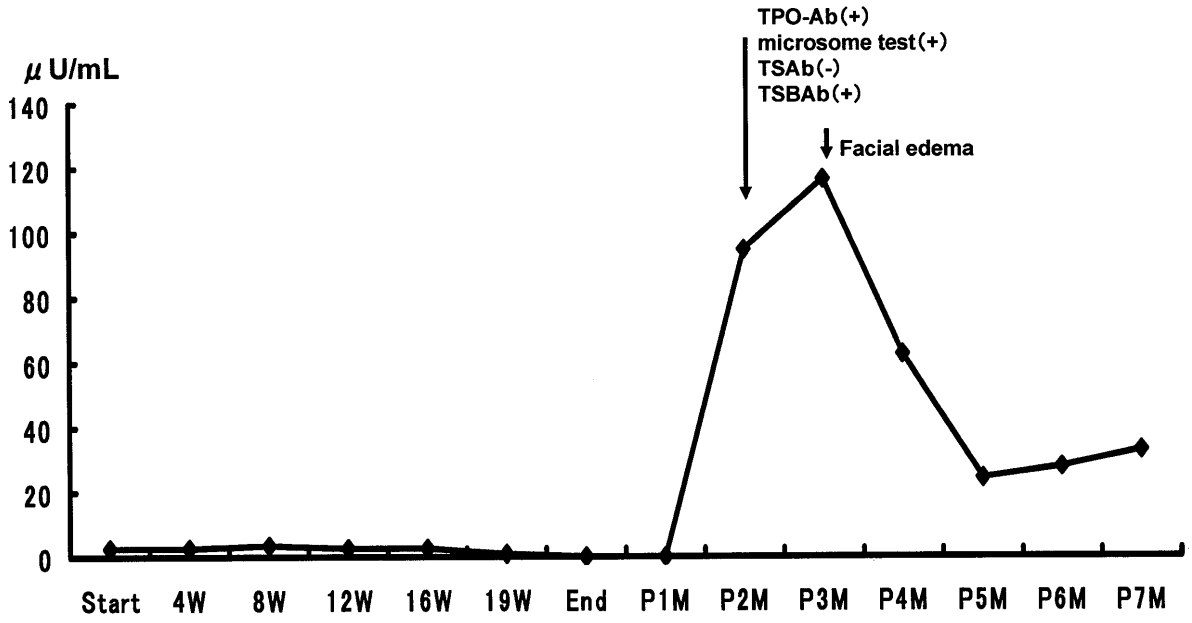

Figure 1-c. Changes of TSH value

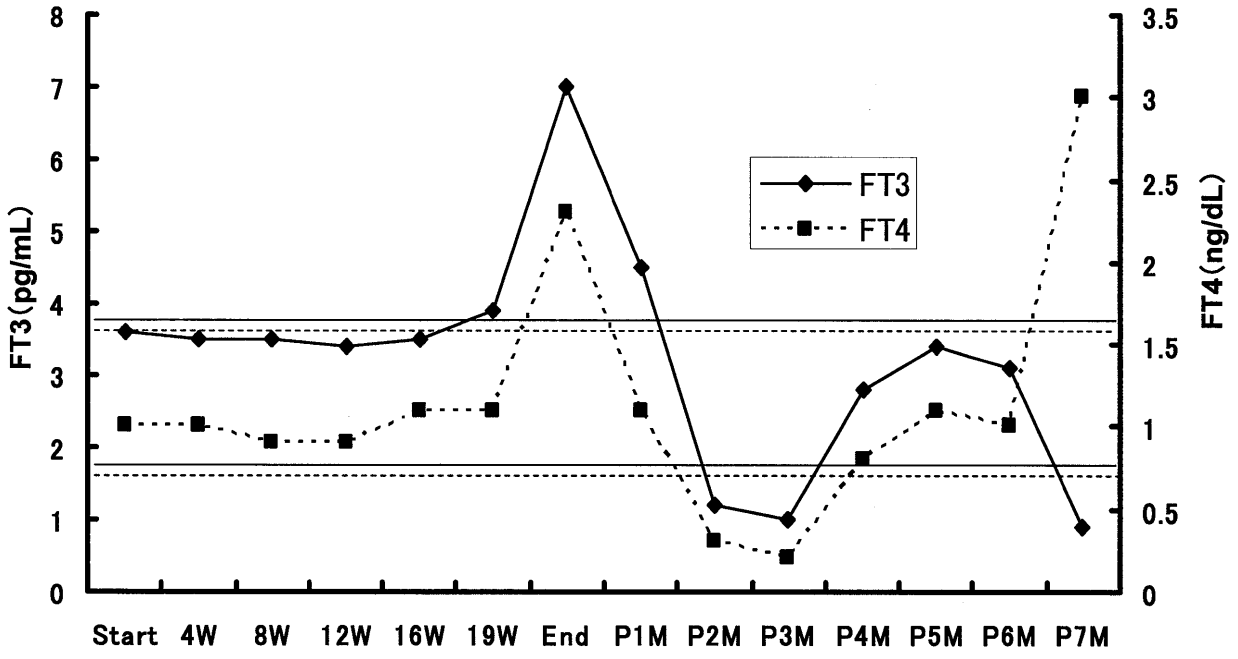

Figure 1-d. Changes of FT3 and FT4 value

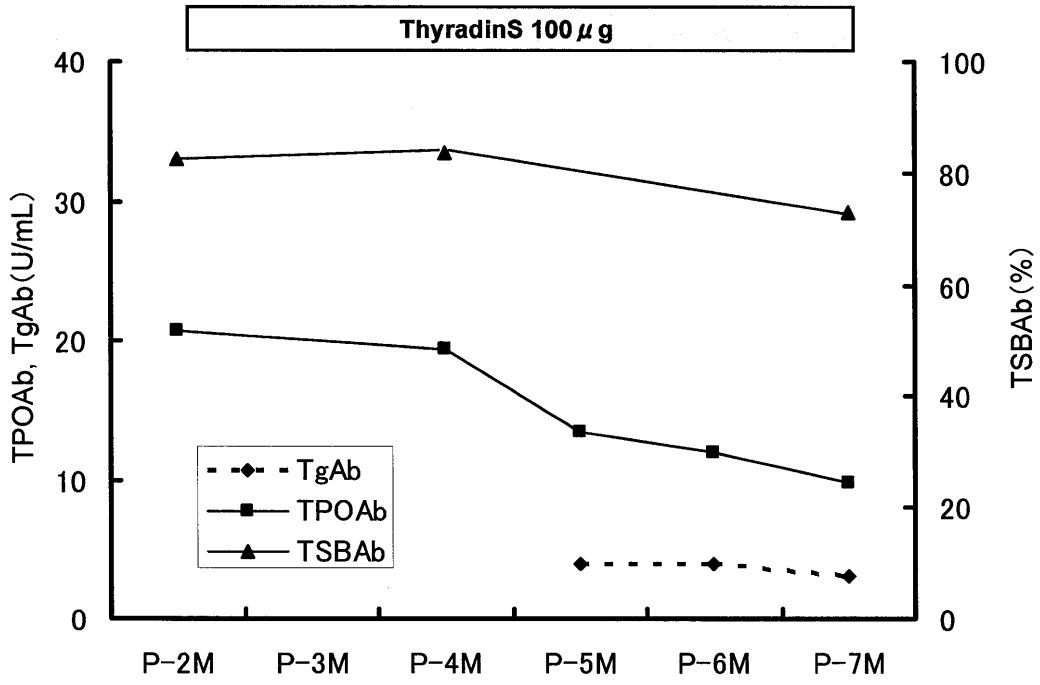

Figure 1-e. Changes of thyroid autoantibodies

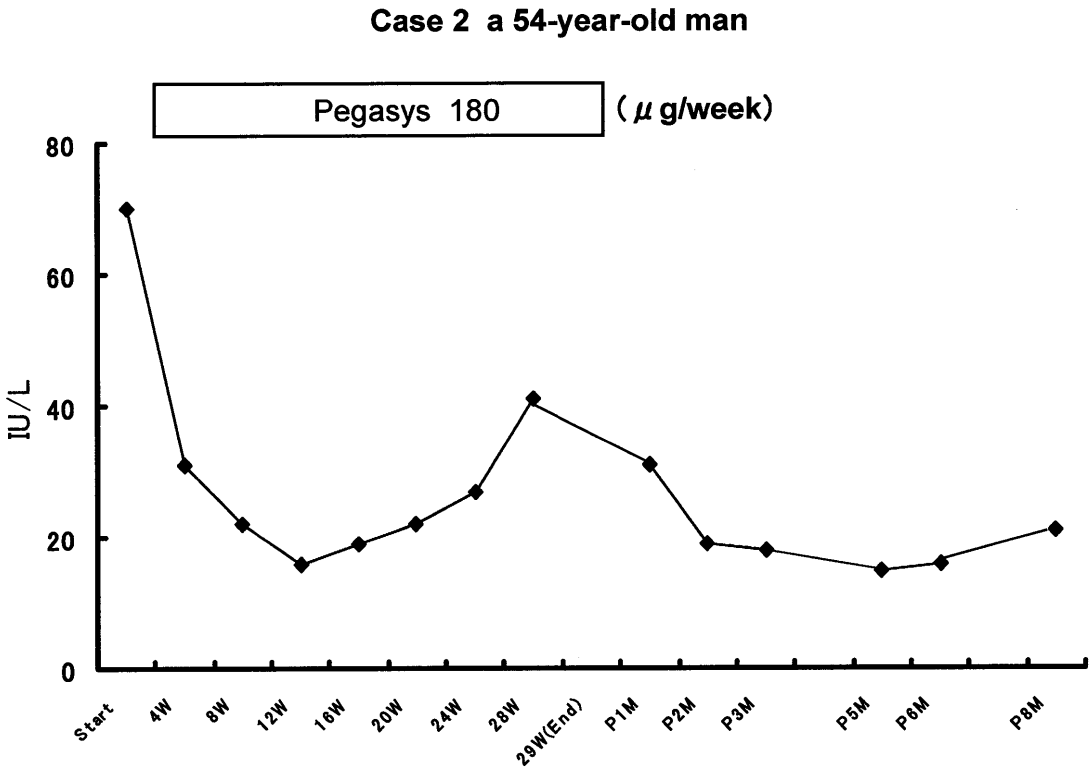

Figure 2-a. Changes of ALT value

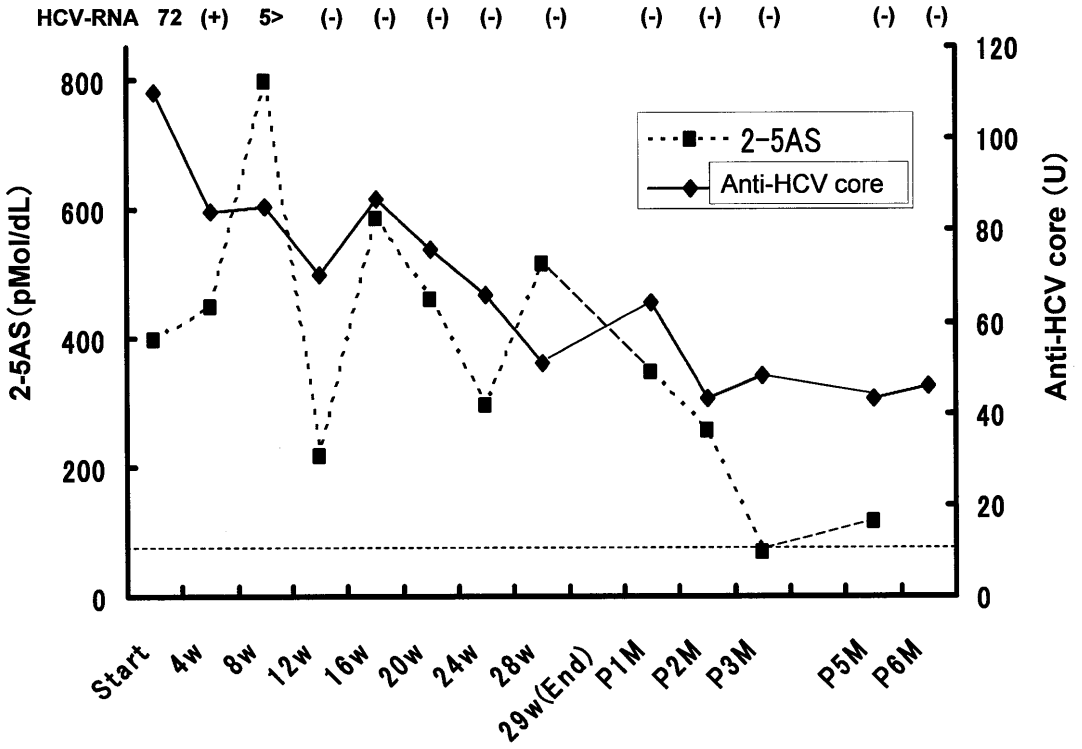

Figure 2-b. Changes of anti-HCV core and 2-5AS activity

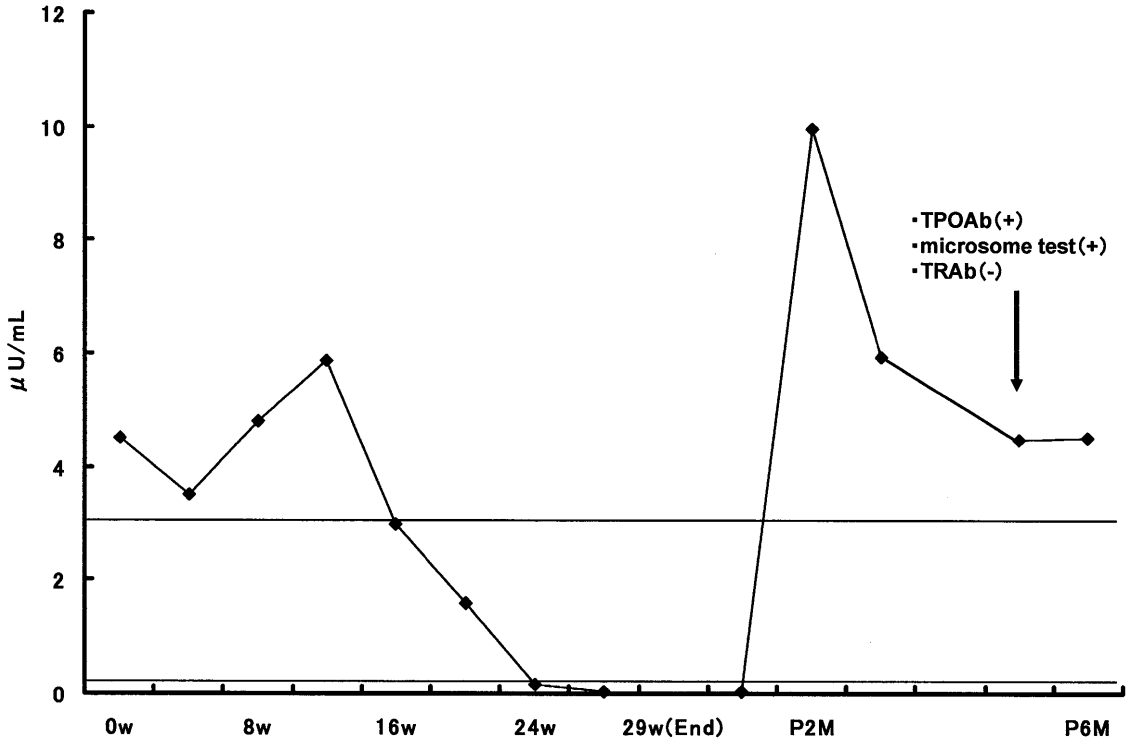

Figure 2-c. Changes of TSH value

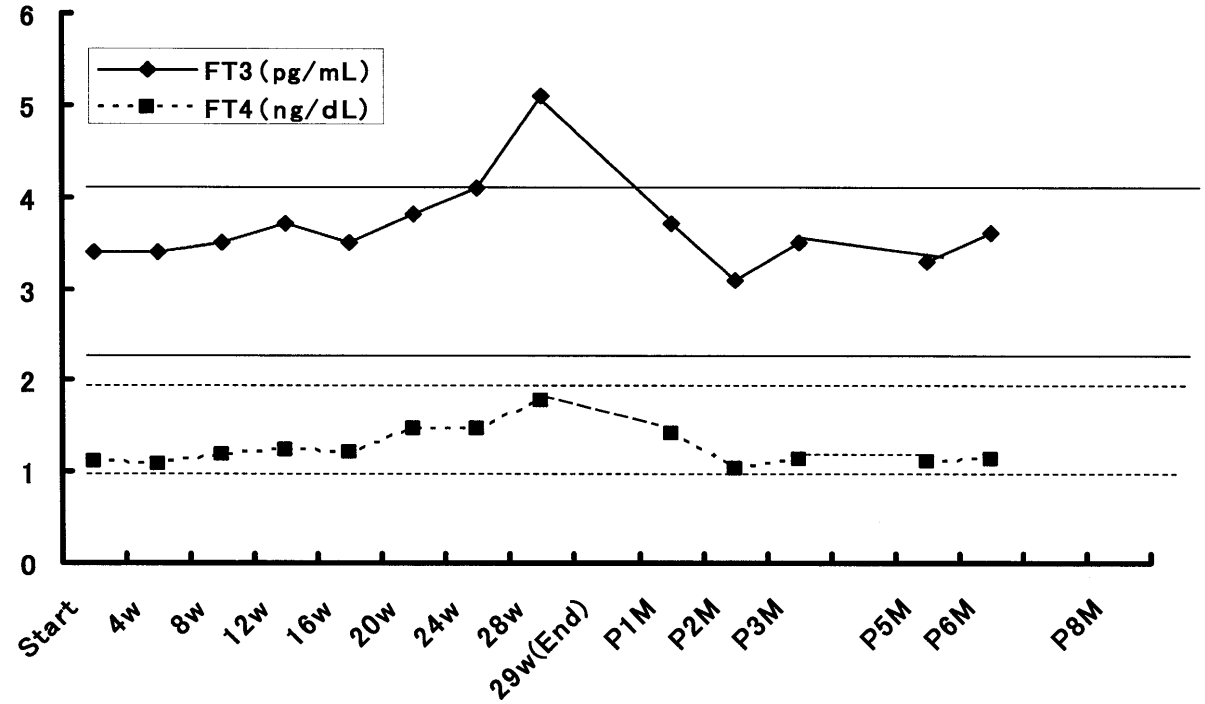

Figure 2-d. Changes of FT3 and FT4 value

tered for 4-24 weeks, and consequently the administration period and total dose were insufficient to completely eradicate the virus, because effective drug concentrations could not be maintained long enough. Hence, the rate of complete virus eradication remained at about 10% for patients with high viral load of HCV genotype Ib infection.

Interferon not only exhibits antiviral activity, but also possesses immunomodulatory functions, such as, suppression of B cell activities, increase in antibody production via T cells, and enhancement of natural killer cell activities; in other words interferon is a biochemical response modifier (BRM). When interferon possessing these actions is administered for therapeutic purposes, one of the disadvantages to the host is the onset or exacerbation of autoimmune disease, such as, thyroid dysfunction [2,3]. Because HCV is lymphotropic, it infects various tissues, besides the liver, and these infected tissues serve as an HCV reservoir to cause continuous infection and reactivation, and immunocomplexes in the circulating blood constantly trigger autoimmune phenomena. In fact, HCV infection has been associated with various extrahepatic manifestations, such as, thyroid disorder, mixed cryoglobulinemia, lymphoproliferative disorders, porphyria cutanea tarda, lichen planus, diabetes mellitus and Sjögren syndrome [4-19]. The onset of autoimmune disease during interferon therapy may be due to the enhancement of such background factors in HCV patients.

Many studies have investigated the relationship between HCV infection and thyroid diseases and autoantibodies, and most studies have found that when compared to the general population, the prevalence of thyroid disease (in particular hypothyroidism) is higher among HCV infected people [12]. Antonelli and colleagues [20] reported that when compared to controls, the prevalence of hypothyroidism, TPO-Ab and Tg-Ab was higher in HCV patients untreated with interferon at 13, 21 and 17%, respectively. Fernandez and colleagues [21] reported the prevalence of TPO-Ab and Tg-Ab in 20 and 11%, respectively, of patients. Furthermore, Prummel and colleagues [22] documented that the relative risk for thyroid disease due to interferon alpha therapy in women was 4.4%, but individual genetic factors would play a large role in its onset. Fernandez and colleagues [21] reported that the prevalence of thyroid dysfunction at the end of interferon alpha therapy was 12%. Deutsch and colleagues [23] found that the risk for treatment induced hypothyroidism was high for patients with thyroid autoantibody before interferon alpha therapy, and antiviral therapy should be relatively contraindicated in patients with thyroid autoantibody even in the absence of clinical symptoms. Others have stated that even in the presence of thyroid disorder prior to therapy, antiviral therapy is possible if thyroid function could be favorably controlled medically [1].

Several studies have investigated the prevalence of thyroid autoantibodies in the general public in Japan. Sasaki [24] conducted thyroid and microsome tests on healthy high school students and reported a prevalence of 0% for boys and 3% for girls. Konno et al. [25] tested for thyroid autoantibodies in healthy adults in Sapporo and reported a prevalence of 6.4% for men and 13.8% for women. Furthermore, Okamura and colleagues [26] measured TSH and FT4 in people 40 years of age or older and reported the prevalence of latent hypothyroidism for men and women at 3.2 and 5.5%, respectively.

In the present study, while the numbers were low, hypothyroidism was confirmed in one patient (2.8%), latent hypothyroidism in six patients (16.7%) and latent hyperthyroidism in one patient (2.8%). These conditions were more prevalent in women, and there were no marked differences with past reports. In addition, although patients having at least one of any thyroid autoantibody or Tg abnormalities were seen in 33.3%, comparable findings could have been obtained if high-sensitivity Tg-Ab and TPO-Ab tests were

employed as the standard measure from the first. One patient with an extremely high microsome test level (102,400-fold) had normal thyroid function, but because the future risk for hypothyroidism is high [27], periodic thyroid hormone tests will be required. In addition, TRAb were detected in 16.7% of patients with mostly low titer and 67% of them had non of thyroid autoantibodies or abnormality of thyroglobulin level, thus suggesting that these patients need to be carefully followed for thyroid disease in the future.

In the present study, Case 1 had hypothyroidism due to peginterferon and ribavirin therapy. A clinical laboratory test at the end of therapy first confirmed latent hypothyroidism, and then the patient experienced overt hypothyroidism. Case 2 had latent hypothyroidism and underwent peginterferon monotherapy. This patient had latent hypothyroidism at the start of therapy but developed latent hyperthyroidism after the start of therapy, and then the pretreatment state was regained after the end of therapy. In general, hyperthyroidism usually precedes hypothyroidism [2]. In the two above mentioned patients, thyroid autoantibodies were not measured prior to therapy, but it was possible that thyroid autoantibodies were present prior to therapy in these patients. Whether thyroid disorders become overt or remain latent is thought to be determined by individual genetic background factors and blood concentrations of interferon and ribavirin. In any case, it will be important to measure thyroid autoantibodies in all patients who are scheduled to undergo interferon therapy and assess the risk of treatment-induced thyroid disorder.

In Case 1, at the onset of hypothyroidism, the ALT level was high, but was lowered by levothyroxine sodium. In Case 2, ALT was mildly elevated during latent hyperthyroidism at the end of interferon therapy, but normalized after the end of therapy. Although some differences were present, ALT increased even though HCV-RNA became undetected in both cases, suggesting that hepatopathy involves autoimmune mechanisms. In fact in Case 1, after experiencing hypothyroidism, levothyroxine sodium lowered TSBAb, TPO-Ab and Tg-Ab and improved ALT. It has been reported that interferon-induced thyroid dysfunction normalizes after therapy in 50% of cases [2] or that long-term hormone replacement therapy would be required for hypothyroidism [28]. Even if hepatitis C is cured, long-term thyroid hormone replacement therapy needs to be avoided as it incurs unexpected physical and psychological stress to patients.

Adverse events considered to result from interferon therapy include relatively innocuous cold-like symptoms, and the more severe interstitial pneumonia, depression, anemia, agranulocytosis, thrombocytopenia, abnormal thyroid function, hair loss and fundus bleeding. It is sometimes difficult to determine whether to continue interferon therapy using conservative treatments. Availability of peginterferon clearly enhanced the therapeutic effect and diminished the subjective symptoms, and once weekly subcutaneous administration is highly convenient. Before peginterferon was available, conventional interferon alpha was administered daily for 2-4 weeks and then every other day for a total of 24 weeks, and as a result, patients needed to be admitted during the early stage of therapy. As a general rule, peginterferon is administered in outpatient department, and physicians only see patients once a week. While the prevalence of subjective symptoms, such as, cold-like symptoms, soon after the start of therapy has clearly decreased, a development clinical trial study found that the prevalence of abnormal clinical laboratory findings has remained unchanged [1]. Since therapy takes longer at 24-48 weeks, persistently high 2-5 AS activity is high, and because the effective interferon concentration is maintained for a long period of time, patients on peginterferon therapy need to be monitored more carefully. In the present

study, the two patients with overt or latent hypothyroidism had persistently high levels of 2-5 AS and HCV-RNA became undetectable. Therefore patients who achieved sustained virological response (SVR) must be closely monitored of thyroid function also after the end of therapy.

Because latent thyroid disorders lack subjective symptoms, they can be easily overlooked without conscious thyroid function tests, and it is possible that thyroid disorders become overt after a certain period of time following interferon therapy. In patients with a past history of interferon therapy, it is recommended to check thyroid autoantibody levels and thyroid function. Thyroid dysfunction and interstitial pneumonia are some of the frequently reported adverse events of interferon therapy, and since interstitial pneumonia directly affect vital prognosis, clinical management and therapeutic guidelines have been mostly established. However, as thyroid dysfunction is often latent and is not linked directly to vital prognosis, its clinical management tends to be neglected. As it has been reported that HCV-induced thyroiditis can lead to thyroid cancer [29], it is necessary to carefully monitor thyroid disorders before, during and after peginterferon therapy, which at present is the standard antiviral therapy for chronic hepatitis C.

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和文要旨

肝外合併症を有さないインターフェロン未治療のC型慢性肝炎36例を対象とし、潜在性甲状腺障害の実態を検討した。対象の内訳は男性13例、女性23例、年齢は32～77歳(中央値62.5歳)～、ALT値の平均は60.8 IU/L(8～188 IU/L)、である。FT4低値例を5.6%に認め、うち1例はTSHが明らかに高値で甲状腺機能低下症と診断された。TSH異常を22.2%に認め、多くが高値例でいずれも女性であった。TRAbおよびTg-Abはそれぞれ16.7%に検出された。ミクロソームテストは9.1%、TPO-Abは5.9%が陽性であった。血中Tg高値例を25.0%に認めた。全体としていずれかの甲状腺自己抗体が陽性か、あるいはTg高値の例は33.3%であり、一般人口に比し高値の傾向であった。潜在性甲状腺機能障害例の多くは機能低下症で女性に多かった。事実われわれも、ペグインターフェロン治療により顕性および不顕性の甲状腺機能低下症を発症した症例を各1例経験した。ペグインターフェロン治療により潜在性甲状腺障害が顕性化する可能性が示唆され、特に治療前甲状腺自己抗体陽性例は、治療開始後も定期的に厳重な甲状腺機能のチェックが必要で、機能悪化を認めた場合は速やかに投与を中止し加療することが重要と考えられた。