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Development of transient thyroid disease and reaction during treatment of chronic hepatitis C with interferon

TOSHINORI KODAMA,[1] SHIGEO KATABAMI,[1,2] KEIICHI KAMIJO,[1] AKIO KATANUMA,[1,2] KENTARO YAMASHITA,[1,2] NAOKI AZUMA,[1,2] TOMOHIRO TAMAKI,[1,2] and AKIRA YACHI[2]

[1] Department of Internal Medicine, Muroran City General Hospital, Tokiwa-cho 2-11, Muroran, 051 Japan
[2] Department of Internal Medicine (Section 1), Sapporo Medical College, Sapporo, 060 Japan

Abstract: Six of 50 (12%) patients with chronic hepatitis C who were treated with interferon developed thyroid disease or an autoimmune thyroid reaction while undergoing treatment. One patient developed silent thyroiditis, with an increase in serum tri-iodothyronine (T_3), thyroxine (T_4), free T_3, free T_4, and markedly suppressed thyroid-stimulating hormone (TSH) levels, accompanied by the appearance of both antithyroglobulin (TgAb) and antimicrosomal antibodies (McAb). One patient developed hypothyroidism in association with moderately elevated TSH levels and high titers of McAb. TSH, TgAb, and McAb levels returned to the initial values at least 4 months after the end of interferon treatment (9 months of follow up). Four patients whose TgAb and/or McAb levels were elevated during treatment with interferon had been diagnosed as having subclinical autoimmune thyroiditis; however, their thyroid function remained in the normal range. These results suggested that treatment with interferon can cause a transient autoimmune thyroid reaction and disease as a side effect.

Key words: thyroid disease, interferon, chronic hepatitis C

Introduction

The hepatitis C virus (HCV) genome has recently been cloned and its nucleotide sequence determined. Hepatitis C virus can now be detected by an immunological assay for serum anti-C100-3 antibody,[1,2] which reacts with a non-structural protein of the hepatitis C virus. More recently, Okamoto et al.[3] developed a system for detecting serum HCV-RNA, using the 5′ non-coding region of HCV as a primer, by the reverse transcribed polymerase chain reaction. The availability of these new serologic assays led us to reassess the effects of interferon therapy in chronic hepatitis C. Clinical trials using interferon in chronic hepatitis C have yielded promising results.[4,5]

Interferon treatment has been accompanied by many acute side effects, such as pyrexia, myalgia, headache, fatigue, and bone marrow suppression. Recent studies have revealed long-term side effects of interferon. Here, we describe thyroid dysfunction and thyroid auto-antibodies that developed during treatment with interferon.

Patients and methods

We studied 50 patients (male:female, 26:24) with chronic active hepatitis C confirmed by liver biopsy. The patients were treated with interferon, using three different preparations; natural beta interferon was used in 11, lymphoblastoid interferon alpha in 17, and recombinant human interferon alpha-2a in 22 (Table 1). All patients were given interferon at a dose of 6 million units daily or three times weekly for 2–6 months. Total doses of interferon were at least 320 million units.

Initial and selected serum samples were tested for HCV-Abs with RIBA-2 (Ortho Diagnostics, Raritan, N.J.). This test incorporates four antigens in the strip, three from the non-structural (5-1-1, c100-3 and C33-c) and one from the core region (C22-3). Serum samples were also tested for HCV-RNA by the reverse transcribed polymerase chain reaction, using the 5′ non-coding region of HCV as a primer.

Serum tri-iodothyronine (T_3), thyroxine (T_4), and thyroid-stimulating hormone (TSH) were measured by

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Table 1. Distribution of patients receiving each type of interferon

	Number of patients	Male : Female
Recombinant human interferon alpha-2a	22	7:15
Lymphoblastoid interferon alpha	17	5:12
Natural beta interferon	11	5:6

chemiluminescent assay (Ciba Corning Diagnostics Co.), and antithyroglobulin antibody (TgAb) and antimicrosomal antibody (McAb) were determined by the particle agglutination method (Fuji Rebio Co. Tokyo, Japan). Patients with thyroid dysfunction or thyroid auto antibodies were also tested for TSH-binding inhibitory immunoglobulin (TBII) and thyroid-stimulating antibody (TSAb). Serum single strand DNA antibodies (ssDNA-Abs) were tested by ELISA (MBL). Serum samples were collected and stored at −20°C until tested.

The patients were divided into two groups, group 1 being characterized by positive titers of TgAb and/or McAb before interferon therapy and group 2 by negative titers of these antibodies before interferon therapy. All patients had euthyroid function before interferon treatment.

Informed consent was obtained from all patients and all details of this study were approved by the Ethics Subcommittee of the Muroran City General Hospital.

Results

Serum T_4 and TSH levels of patients before and after treatment with the three kinds of interferon are shown in Table 2. No significant difference was seen in T_4 and TSH among the three kinds of interferon. Thyroid reaction and dysfunction were observed in 6 of the 50 patients during long-term interferon treatment.

Group 1 consisted of four patients (8.5%). Their thyroid function was normal, without goiter or subjective complaints characteristic of subclinical autoimmune thyroiditis. The titers of TgAb and/or McAb were elevated during interferon treatment, but thyroid function tests remained in the normal range. Three of these four patients received recombinant human interferon alpha-2a and the other patient received lymphoblastoid interferon alpha (Table 3).

Group 2 consisted of 46 patients, of whom 2 (4.3%) showed transient thyroid dysfunction during interferon treatment. In one patient (patient 5) latent hypothyroidism characterized by normal serum T_4 levels and moderately elevated TSH occurred during interferon treatment. McAbs were detected at a dilution of 1:6400. Thyroid function spontaneously recovered and reached normal levels 16 weeks after the end of interferon treatment (Table 4). Serum ssDNA-Ab levels became elevated. These clinical and laboratory findings led to us the diagnosis of transient hypothyroidism developing during long-term interferon treatment. Serum aminotransferase levels decreased to the normal range, but serum HCV-RNA remained positive.

In another patient (patient 6), a transient increase in serum thyroid hormone levels appeared after 12 weeks. Endocrine examination at that time disclosed an increase in serum T_3, T_4, free T_3, and free T_4 levels, and markedly suppressed TSH levels. Both TgAb and McAb were detected at a dilution of 1:400. TBII and TSAb remained negative. These clinical features and laboratory findings led to the diagnosis of silent thyroiditis developing during long-term interferon treatment. Serum T_3, T_4, free T_3, free T_4, and TSH spontaneously recovered and reached normal levels 2 months after the onset of thyrotoxicosis through the subclinical hypothyroid stage. In addition, TgAb and McAb also returned to negative 4 weeks after the end of interferon treatment (Table 4). This

Table 2. Thyroid function before and after interferon therapy

	T_4 (before)	T_4 (after)	TSH (before)	TSH (after)
Normal value	5.4–10.8 (μg/dl)		0.31–2.82 (μU/ml)	
IFNα2a	10.9 ± 3.6	9.1 ± 2.6	2.1 ± 2.8	3.9 ± 6.9
IFNα	11.4 ± 3.6	10.5 ± 3.4	2.4 ± 2.0	2.2 ± 1.3
IFNβ	11.7 ± 3.3	11.3 ± 3.7	1.6 ± 0.7	1.8 ± 0.8
Total	11.2 ± 3.5	10.3 ± 3.0	2.1 ± 2.3	3.0 ± 5.2

IFNα2a, Recombinant human interferon alpha-2a; *IFNα*, lymphoblastoid interferon alpha; *IFNβ*, natural beta interferon; *TSH*, thyroid-stimulating hermone

Table 3. Thyroid autoantibodies and thyroid function in four patients with subclinical autoimmune thyroiditis during interferon therapy

Normal value	IFN	T_4 5.4–10.8 (μg/dl)	TSH 0.31–2.82 (μU/ml)	TgAb <100	McAb <100	Diagnosis
Patient 1						
Before	α2a	9.4	5.12	0	× 800	Subclinical
Week 8		10.1	2.02	0	× 1600	autoimmune
Week 16		10.2	1.33	0	× 1600	thyroiditis
Patient 2						
Before	α2a	11.2	2.46	0	× 100	Subclinical
Week 12		7.9	1.20	× 100	× 6400	autoimmune
Week 24		9.7	1.05	× 100	× 6400	thyroiditis
Patient 3						
Before	α	13.8	2.50	× 400	× 6400	Subclinical
Week 8		13.6	3.17	× 1600	× 6400	autoimmune
Week 24		13.7	3.16	× 1600	× 6400	thyroiditis
Patient 4						
Before	α2a	7.9	2.46	0	× 400	Subclinical
Week 12		8.6	0.69	0	× 6400	autoimmune
Week 24		9.7	1.05	× 400	× 25 600	thyroiditis

α2a, Recombinant human interferon alpha-2a; *α*, lymphoblastoid interferon alpha

Table 4. Thyroid autoantibodies and thyroid function in a patient with hypothyroidism and a patient with silent thyroiditis during interferon therapy

Normal value	IFN		T_4 5.4–10.8 (μg/dl)	TSH 0.31–2.82 (μU/ml)	TgAb <100	McAb <100	Diagnosis
Patient 5	Before treatment		12.2	0.88	0	0	
	Week 12	α2a	8.9	1.18	0	0	Hypothyroidism
	Week 24		6.5	30.98	0	× 1600	
	16 Weeks after end of IFN		9.8	0.38	0	0	
Patient 6	Before treatment		12.3	0.77	0	0	
	Week 12	α2a	23.4	0.05>	× 400	× 400	Silent thyroiditis
	Week 24		12.0	0.08	× 400	× 400	
	4 Weeks after end of IFN		9.96	1.12	0	0	

IFN, Interferon; *α2a*, recombinant human interferon alpha-2a

patient, who developed silent thyroiditis, responded well to interferon therapy; serum aminotransferase levels decreased to the normal range and HCV-RNA became undetectable. Serum ssDNA-Ab was detected after interferon treatment.

Discussion

Since Burman et al.[6] reported hypothyroidism induced by interferon treatment of breast cancer, there have been 48 reported cases of thyroid dysfunction, including 8 of Graves' disease, 26 of hypothyroidism, and 13 of transient thyrotoxicosis developing during and after interferon treatment.[8–17] These findings indicate that the interferon therapy probably induced thyroid disease indirectly by stimulating the expansion of a clone of autoantibody-producing B lymphocytes and that the induced disease varied according to the specificity and characteristics of the autoantibody.

The mechanism by which interferon induces autoimmune reactions is still unclear. The effects of interferon on the immune system include suppression of lymphocyte proliferation in vitro and enhancement of T cell, as well as natural killer cell, cytotoxicity. Interferon also increases the cell surface expression of MHC class I and II antigens.[10] Recent reports have suggested that prolonged interferon-alpha therapy may induce autoimmune reactions. Mayet et al.[19] reported that antinuclear antibodies appeared in 11 (35.5%), smooth muscle antibodies in 21 (67.7%), antithyroglobulin antibodies in 9 (29.1%), and antimicrosomal antibodies in 5 (16.1%) of 31 patients receiving interferon-alpha. They also found that the appearance of these autoantibodies was not correlated with disease activity. Therefore, it appears that interferon therapy may

cause immunological changes as side effects. Our four patients whose TgAb and/or McAb were elevated during treatment with interferon had been diagnosed as having subclinical autoimmune thyroiditis. However, their thyroid function remained in the normal range. Their TgAb and/or McAb was thus not correlated with thyroid disease activity.

Lisker-Melman et al.[13] reported that thyroid disease developed more commonly in patients with chronic hepatitis B. The reason for this phenomenon may be that patients with chronic hepatitis C are treated for longer periods than patients with hepatitis B.

Which type of interferon is most likely to produce autoimmune disease remains unclear. Pagliacci et al.[20] reported that interferon-beta treatment did not induce thyroid autoimmune disease. Our results support their contention that thyroid autoimmune disease is not a frequent side effect.

Marcellin et al.[10] reported two cases of hypothyroidism in patients with chronic hepatitis C treated with interferon. In one patient, interferon induced hypothyroidism in the absence of pre-existing thyroid dysfunction. Thyroid function did not return to normal after withdrawal of interferon, and a permanent substitute treatment was needed. They also reported that McAbs were detected at a dilution of 1:25 600 9 days after the end of interferon treatment, then disappeared 6 months later. The thyroid function of patients with silent thyroiditis and hypothyroidism returned to normal after the end of interferon treatment. A recent report by Berris and Feinman[21] pointed out that transient thyrotoxicosis with subsequent hypothyroidism possibly developed in patients treated with interferon. Therefore, it is conceivable that interferon might induce a transient effect on thyroid function.

We have described have a case of transient silent thyroiditis, a case of transient hypothyroidism, and four cases of subclinical autoimmune thyroiditis following interferon therapy for chronic type C hepatitis. Since interferon therapy caused the appearance or detection of thyroid antibodies and ssDNA-Abs, it is reasonable to say that interferon therapy caused immunological change. Although the exact etiology of the thyroid reaction still remains obscure, recent evidence suggests that an autoimmune process must be involved.

In conclusion, it is necessary to pay careful attention to the presence of autoantibodies to the thyroid and to changes in thyroid function before and during interferon therapy.

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