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Original Article

Clinical Trial of Four Weeks of Combination Therapy with Low-dose Methimazole and a Cholesterol Absorption Inhibitor as the Initial Treatment for Childhood-onset Graves' Disease

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Abstract. The initial treatment of childhood-onset Graves' disease is based on the result of clinical trials of adult-onset disease. The major adverse events associated with methimazole, the only medication approved for childhood-onset disease in Japan, are considered to depend on the dose, and the risk of adverse events is increased in patients requiring higher doses for initial treatment. The serum levels of thyroid hormones are partially dependent on the enterohepatic circulation, especially under thyrotoxicosis. Cholesterol absorption inhibitors suppressing the enterohepatic circulation have the possibility of controlling thyrotoxicosis. In this clinical trial, 13 patients with childhood-onset Graves' disease (5.5 to 15.3 yr old) were divided into three treatment groups: low-dose (0.25 mg/kg/d) methimazole monotherapy, high-dose (1.0 mg/kg/d) methimazole monotherapy, and combination (low-dose methimazole + a cholesterol absorption inhibitor) therapy. The therapeutic efficacy was determined based on the rates of decrease of thyroid hormones for four weeks. The high-dose methimazole regimen was superior in efficacy to the low-dose methimazole regimen, while the combination therapy demonstrated effects equal to those of the high-dose monotherapy. Therefore, combination therapy with a cholesterol absorption inhibitor can improve thyrotoxicosis, and the dose of methimazole can be reduced in the initial treatment of child-onset Graves' disease.

Key words: Graves' disease, childhood-onset, methimazole, cholesterol absorption inhibitor, colestimide

Introduction

Graves' disease is a well-known condition; however, few clinical trials has been performed for childhood-onset disease. The guideline for treatment of childhood-onset Graves' disease published in Japan in 2008 was mainly based on clinical trials of adult-onset disease and the therapeutic experience of pediatricians, and it was recommended that methimazole, an antithyroid drug, should be administered at 0.5–

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1.0 mg/kg/d as the first-choice drug (1). Although propylthiouracil is also an effective antithyroid drug, its use is contraindicated in children because it causes severe liver dysfunction (2, 3). Methimazole is the only medical drug approved for use in childhood-onset Graves' disease in Japan; however, it is also associated with adverse events, including liver dysfunction (3). The adverse events associated with methimazole are considered to be dependent on the dose used (4), particularly fatal agranulocytosis (5, 6). The risk of adverse events is generally increased in the early stage of treatment because the initial dose is high in order to resolve the thyrotoxicosis; therefore, high-dose therapy is generally avoided (7).

Thyroid hormones are fat-soluble hormones that are partially excreted into bile and are reabsorbed from the intestines (enterohepatic circulation), especially in rats (8). Under thyrotoxicosis, the excretion of thyroid hormones into the intestines increases in order to maintain the thyroid hormone concentration in the liver (9). In humans, the enterohepatic circulation is not considered to be significant (10). However, it has been reported that cholestyramine, a cholesterol absorption inhibitor that inhibits the enterohepatic circulation, dramatically reduces the intestinal absorption of levothyroxine in humans (11). Previous articles have demonstrated that combination therapy with antithyroid drugs and cholesterol absorption inhibitors is effective for treating thyrotoxicosis in patients with adult-onset Graves' disease (12–16) (Table 1). Taken together, these reports suggested that the enterohepatic circulation might have a more significant function under thyrotoxicosis in human.

We hypothesized that using a cholesterol absorption inhibitor in the initial treatment of childhood-onset Graves' disease would allow for the use of a lower initial dose of methimazole. We examined the effects of combination therapy using low-dose methimazole and a cholesterol absorption inhibitor and compared the outcomes of patients treated with low-dose or high-dose methimazole monotherapy in this study.

Methods

We examined 13 patients with Graves' disease whose serum levels of free T3 were higher than 10 pg/ml. All patients visited our hospital, Okinawa Prefectural Nanbu Medical Center & Children's Medical Center, to receive the initial treatment between April 2009 and March 2011. The subjects consisted of 11 females and two males. The age at onset of Graves' disease ranged from 5.5 to 15.3 yr of age. Graves' disease was diagnosed based on the presence of thyrotoxicosis with free T3 dominance, positive TSH receptor antibodies (TRAb), and a diffuse and increased Doppler blood flow in the thyroid gland.

The thirteen patients were distributed sequentially into the following three treatment groups: Group A received monotherapy with low-dose (0.25 mg/kg/d; maximum 10 mg/d) methimazole, Group B received monotherapy with high-dose (1.0 mg/kg/d; maximum 30 mg/d) methimazole, and group C received combination therapy with low-dose methimazole and a cholesterol absorption inhibitor (colestimide). The colestimide was administered at 1 g per day for four weeks; this dose is approximately one-third of the standard dose used for hypercholesterolemia in adults. The daily doses of methimazole and colestimide were divided in two and were administered at the same time after meals. A beta-blocker was also administered in all patients during the clinical trial. This study was permitted by our Hospital Ethics Committees. Additionally, sufficient informed consent was obtained for all patients.

Blood tests were performed in the 13 patients at the initial visit on which the treatment was started, two weeks after the start of treatment, and four weeks after the start of treatment. The serum TSH, free T3 and free T4 levels were examined as the thyroid function. The rates of decrease of thyroid hormones were

Table 1 Summary of the previous reports showing that the cholesterol absorption inhibitors have efficacy in treating thyrotoxicosis in adult-onset Graves' disease

Author Year, Ref.	Number of cases	Age (yr old)	ATDs	CAIs therapy	Study designs	Efficacy of treatment
Solomon 1993 (12)	15	38.5 ± 13	MMI	Cholestyramine 3 g QID for 2 wk	MMI 15–60 mg + Phase I: cholestyramine or placebo powder (for 2 wk) Phase II: placebo powder or cholestyramine (for 2 wk) (crossed-over treatment)	Phase I Cholestyramine effective Phase II Cholestyramine not significantly effective
Mercado 1996 (13)	30	33 ± 10	MMI	Cholestyramine 3 g TID for 2 or 4 wk	Group I: MMI 30 mg + cholestyramine (for 4 wk) Group II: MMI 30 mg Group III: MMI 30 mg + cholestyramine (for 2 wk)	Group I ≈ III >II ↓ 2 wk later Group I > III ≈ II
Hagag 1998 (14)	92	45.1 (over 18)	MMI	Colestipol 5 g QID for 2 wk	Group I: MMI 30 mg + colestipol Group II: MMI 30 mg Group III: MMI 15 mg + colestipol	Mild thyrotoxicosis Group III > I ≈ II Severe thyrotoxicosis Group I > II ≈ III
Tsai 2005 (15)	30	31.3 (18 – 53)	PTU	Cholestyramine 4 g BID for 4 wk	Group I: PTU 200 mg + cholestyramine Group II: PTU 200 mg	Group I > II
Kaykhaei 2008 (16)	45	31.4 ± 5.2 (20 – 54)	MMI	Cholestyramine 1 or 2 g BID for 4 wk	Group I: MMI 30 mg + cholestyramine (1 g BID) Group II: MMI 30 mg + cholestyramine (2 g BID) Group III: MMI 30 mg + placebo powder	Group I ≈ II > III
our cases 2013	13	12.1 ± 2.7 (5.5 –15.3)	MMI	Colestimide 0.5 g BID for 4 wk	Group A: MMI 0.25 mg/kg (maximum 10 mg) Group B: MMI 0.1 mg/kg (maximum 30 mg) Group C: MMI 0.25 mg/kg (maximum 10 mg) + colestimide	Group B ≈ C > A

Ref., reference number; ATDs, antithyroid drugs; CAIs, cholesterol absorption inhibitors; MMI, methimazole; PTU, propylthiouracil; QID, four times dairy; TID, three times dairy; BID, twice daily.

Table 2 Characteristics, initial thyroid functions, and initial treatments in 13 patients with child-onset Graves' disease

Group	Patient number	Age at onset (yr old)	Sex	Thyroid function at onset			Medication	
				Free T3 (pg/ml)	Free T4 (ng/dl)	TRAb (IU/l)	Methimazole	Colestimide
Group A Low-dose Methimazole	1	10.5	Female	13.39	3.42	10.3	7.5 mg	—
	2	10.4	Female	>30	>10	125	10 mg	—
	3	15.3	Male	17.42	5.32	45.6	10 mg	—
	4	11.6	Female	13.22	3.35	8.8	10 mg	—
	Mean ± SD	12.0 ± 2.3		18.51 ± 7.90	5.52 ± 3.12	47.4 ± 54.4		
Group B High-dose Methimazole	5	5.5	Female	15.11	4.45	16.3	15 mg	—
	6	10.5	Female	>30	>10	7.1	25 mg	—
	7	15.1	Male	23.33	6.93	26.9	30 mg	—
	8	11.4	Female	21.69	7.52	17.2	30 mg	—
	Mean ± SD	10.6 ± 4.0		22.53 ± 6.11	7.23 ± 2.28	16.9 ± 8.1		
Group C Low-dose Methimazole + Colestimide	9	12.2	Female	13.87	3.34	4.1	10 mg	1 g
	10	15.2	Female	28.28	6.73	13.7	10 mg	1 g
	11	14.2	Female	16.85	4.9	18	10 mg	1 g
	12	11.4	Female	>30	8.98	10.2	10 mg	1 g
	13	13.5	Female	18.56	6.34	22.5	10 mg	1 g
	Mean ± SD	13.3 ± 1.5		21.51 ± 7.19	6.06 ± 2.11	13.7 ± 7.1		

There are no statistical differences between the groups in initial status, age at onset or the levels of free T3, free T4 and TRAb.

calculated in all three groups (13, 16). Because the rates of decrease of thyroid hormones became underestimate in cases of mild thyrotoxicosis, the patients with relative higher serum levels of free T3 were extracted in this study. In Group C, the thyroid function was also evaluated four weeks after suspending the colestimide treatment. The serum total cholesterol levels were compared at two and four weeks after the start of treatment, because the serum total cholesterol levels generally are strongly affected by the high-level thyrotoxicosis at the time of diagnosis.

All of the results are expressed as the mean ± SD. Correlations between the data were assessed using Pearson's correlation coefficient. Statistical significance was assessed using the Student's *t*-test. A p value of < 0.05 was considered to be significant.

Results

The background and initial data of the 13 patients are shown according to the treatment groups. No background or initial data were significantly different between the groups (Table 2). With regard to the levels of TRAb, although one patient in Group A (patient No. 2 in Table 2) exhibited an extremely high level, there were no significant differences between Groups B and C. Moreover, the results of statistical processing revealed no changes to whether there were significant different or not even if patient No. 2 was excluded from this study.

As an index of the therapeutic efficacy, the rates of decrease of both free T3 and free T4 were determined. In Group A (low-dose), the free T3 and free T4 levels were decreased by approximately 50% at four weeks. In Group B (high-dose), the free T3 and free T4 levels were decreased by approximately 80–90% at four weeks (Fig. 1).

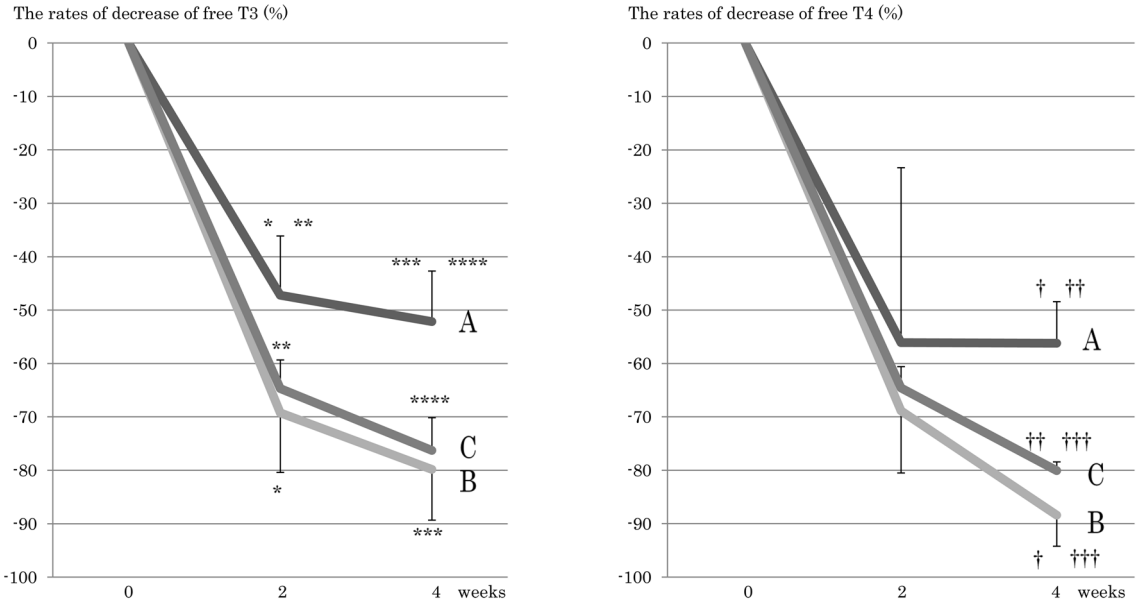

Fig. 1 The rates decrease of thyroid hormones in each group during the four weeks after the initiation of treatment. A, B, and C indicate each treatment group. The data are presented as the mean ± SD. * $p<0.05$, comparing Group A *vs.* Group B. ** $p<0.05$, comparing Group A *vs.* Group C. *** $p<0.005$, comparing Group A *vs.* Group B. **** $p<0.005$, comparing Group A *vs.* Group C. † $p<0.005$, comparing Group A *vs.* Group B. †† $p<0.001$, comparing Group A *vs.* Group C. ††† $p<0.05$, comparing Group B *vs.* Group C.

When Group A was compared with Group B statistically, an obvious dose-dependent effect of treatment was observed, with the exception of the decreasing rate of free T4 at two weeks.

In Group C (combination), the free T3 and free T4 levels were decreased by approximately 80% at four weeks. This efficacy was statistically superior to that observed in Group A, which received the same dose of methimazole. Group C also had the same efficacy as Group B, although the dose of methimazole was lower than that of Group B; Group C was statistically inferior to Group B only in terms of the decreasing rate of free T4 at four weeks (Fig. 1).

In the individual longitudinal evaluations, the free T3 and free T4 levels remained elevated above the normal range at four weeks in all of the patients in Group A, while the levels reached the normal range in many patients in Groups B and C. In most of the patients in Group B, the free T4 levels were lower than the normal value at four weeks (Fig. 2). Conversely, the TSH levels were increased above the normal range at four weeks in Group B, and remained lower in Group C (data not shown). In one of the five patients in Group C, the thyroid function was slightly elevated at four weeks after suspending colestimide treatment, although the thyroid functions continued to decrease in the other four patients (Table 3, Fig. 3).

The serum total cholesterol levels were increased along with improvement of thyrotoxicosis when the values obtained at two weeks and four weeks were compared. In Group C, the serum total cholesterol levels were similarly increased despite treatment with a cholesterol absorption inhibitor (Fig. 4). There were no clinical symptoms regarded to be adverse events of the cholesterol absorption inhibitors during the four weeks of this clinical trial. Adverse events relevant to methimazole were not confirmed in any group.

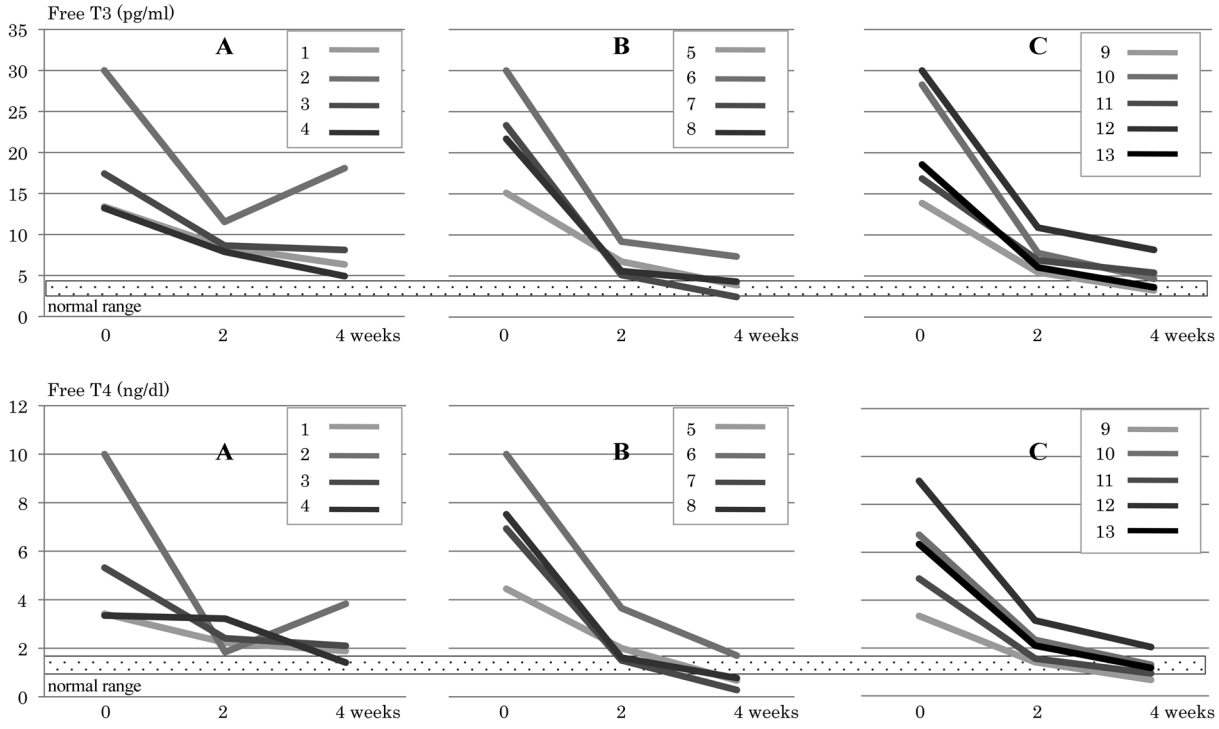

Fig. 2 Individual changes in the thyroid hormone levels in each group during the four weeks after the initiation of treatment. A, B and C indicate each treatment group. The legend numbers indicate each patient.

Discussion

This clinical trial showed that the effects of methimazole are dependent on the dose of the medication and that a cholesterol absorption inhibitor is effective in improving thyrotoxicosis in children. The efficacy of a cholesterol absorption inhibitor was documented for the first time in children in the present study, and no difference was observed compared with the previous reports in adults (12–16).

We referred to the previous clinical trials in adults, and designed this study in which the cholesterol absorption inhibitor was administered at one-third of the standard dose used for hypercholesterolemia in adults for four weeks. In the early reports, the dose of cholesterol absorption inhibitors for thyrotoxicosis was equal to the standard dose used for hypercholesterolemia in adults (12–14), but it tended to be set lower gradually. The use of either only one-half or one-quarter of the standard dose used for hypercholesterolemia in adults had been found to be effective for the purpose of supporting antithyroid drugs (15, 16). The first report using cholesterol absorption inhibitors for hypertoxicosis indicated that the duration of efficacy of cholesterol absorption inhibitors was restricted to the first few weeks after the start of the treatment (12). Another report suggested that four weeks of treatment is associated with superior results compared with that observed following two weeks of treatment (13). The administration of a cholesterol absorption inhibitor beyond four weeks would lead to no further improvements because the reabsorption efficiency of thyroid hormones would no longer be of importance after thyrotoxicosis is improved by the antithyroid drugs.

It has been considered that childhood-onset Graves' disease is resistant to antithyroid drugs and is more refractory than adult-onset disease

Table 3 Averages of the thyroid hormone levels before and after suspending colestimide treatment in Group C

	At the time of suspending colestimide	At four weeks after suspending colestimide	
Free T3	5.02 ± 1.96	4.13 ± 1.13	pg/ml
Free T4	1.22 ± 0.52	0.83 ± 0.48	ng/dl

There are no statistical differences in thyroid hormone levels between before and after suspending colestimide.

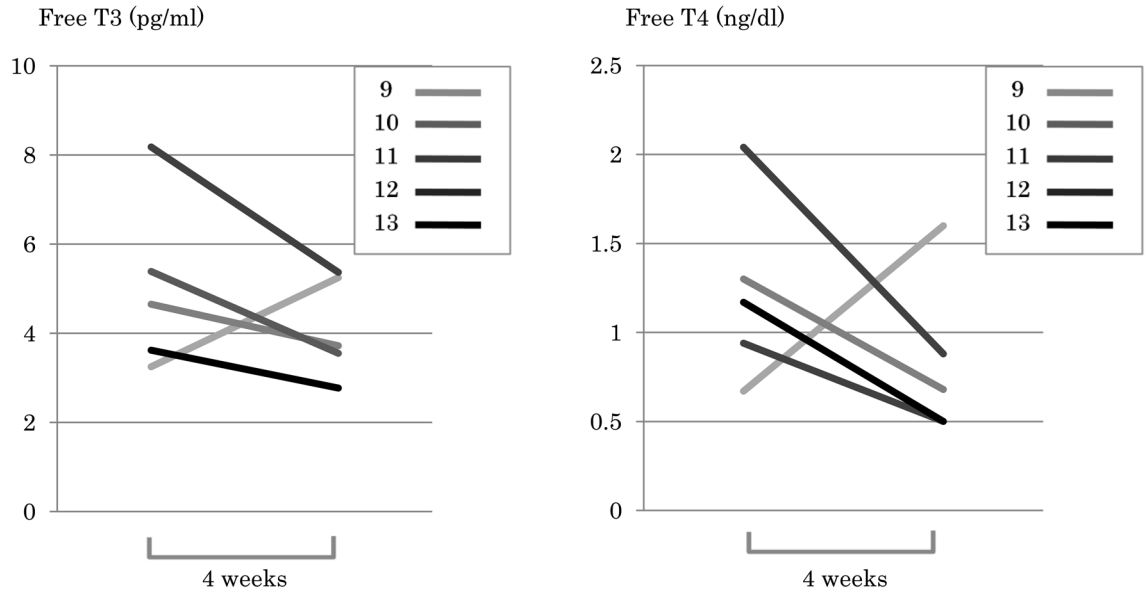

Fig. 3 Changes in the thyroid hormone levels before and after suspending colestimide treatment in Group C. The legend numbers indicate each patient.

(17); therefore, childhood-onset disease must be distinguished from adult-onset disease, especially when considering the treatment. Since there have been few clinical trials of childhood-onset disease, a standard treatment for childhood-onset Graves' disease has been under consideration. In Japan, the guideline for treatment of childhood-onset Graves' disease issued in 2008 is now under revision, and new contents are expected.

It is important to determine the appropriate dose of methimazole for the initial treatment of Graves' disease in childhood without causing adverse events, and it would be ideal to start the treatment using a lower dose of methimazole in terms of preventing adverse events. Regarding this point, the combination therapy with the efficacy equal to the high-dose of methimazole is appropriate as the initial therapy that should be regulated as low-dose as possible.

Another benefit of low-dose methimazole is prevention of the risk of overtreatment. Reducing the dose of antithyroid drugs in case of overtreatment involves the risk of failure that the levels of thyroid hormones will remain low or that thyrotoxicosis will recur because the adjustment method used for dose reduction is indefinite. Indeed, the combination therapy did not result in overtreatment like the high-dose methimazole monotherapy at four weeks

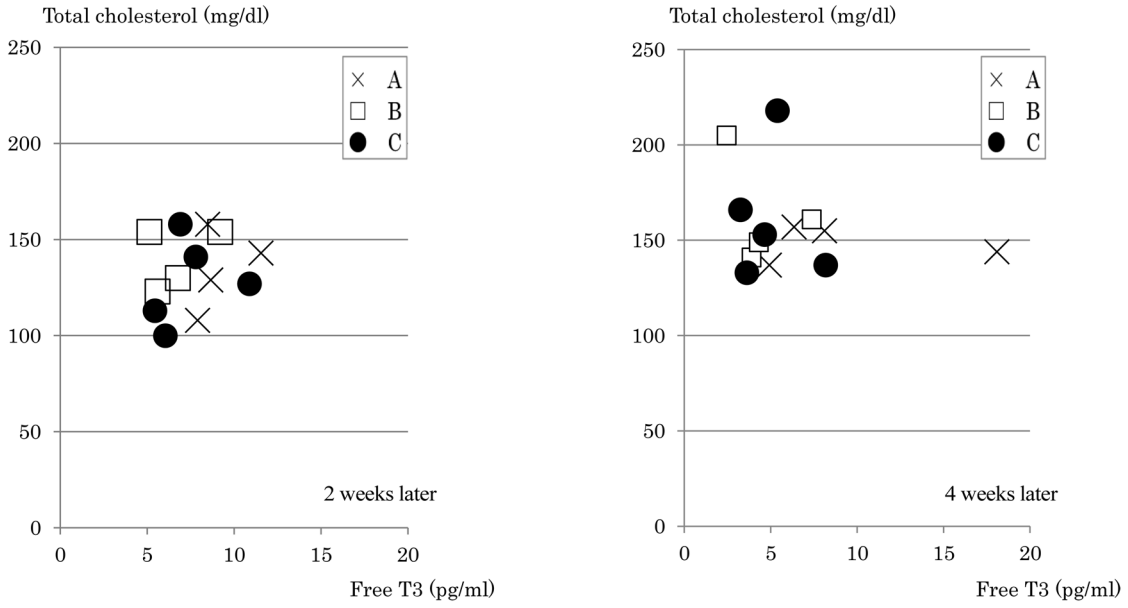

Fig. 4 Relationship between the serum total cholesterol and FT3 levels: comparison at two weeks (left) and at four weeks (right) after the initiation of treatment. A, B and C indicate each treatment group.

after the start of treatment, and the fluctuation in thyroid hormone levels was trivial after suspending cholesterol absorption inhibitors. Consequently, the combination therapy is considered to be effective and safe as the initial therapy for child-onset Graves' disease.

When administering combination therapy with a cholesterol absorption inhibitor, the dose of methimazole used in the initial treatment can be reduced with similar efficacy. The additional use of a cholesterol absorption inhibitor is one option for the initial treatment of childhood-onset Graves' disease. This clinical trial, however, had limitations such as the small numbers of patients and lack of randomization. Further studies are therefore needed.

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