NOTE

Effectiveness of a Short-Term Steroid Treatment on the Reduction in Goiter Size in Antithyroid Drug-Treated Patients with Graves' Disease

TORU MORI, HIDEO SUGAWA, SHINJI KOSUGI, MICHIKO UEDA,
DAISUKE INOUE, AND TAKASHI AKAMIZU*

*Department of Laboratory Medicine and *2nd Division of Internal Medicine,
Kyoto University School of Medicine, Kyoto 606-01, Japan*

Abstract. Reduction of goiter size is one of the criteria necessary to determine clinical remission in antithyroid drug (ATD)-treated Graves' patients. To facilitate goiter reduction or to achieve quick remission, a short-term steroid treatment was administered to 5 Graves' patients. These patients had been treated with ATD for a considerable period of time, had maintained euthyroidism with negative or weak thyrotropin-binding inhibitor immunoglobulin (TBII), but still had an enlarged goiter and remained T₃ unsuppressive. Betamethazone was initially given 1.5 mg daily and then gradually tapered to 0 mg for 3 months. Compared to the 6-month observation period or the pre-medication period, goiter reduction exceeding 0.7 cm was achieved in all 5 patients during the steroid treatment. These reductions partly reversed to an extent smaller than pre-treatment levels in 2 patients, but continuous goiter reductions were observed for at least 3 months after steroid cessation in 3 patients. In 2 of these reduced goiter patients, T₃ suppressibility was confirmed, and they were diagnosed in remission. During steroid administration, serum T₃ and TSH concentrations were lowered but reversed shortly, serum fT₄ concentrations did not change, and TBII levels became negative in all patients including the 2 with weak positive values before the treatment. In conclusion, a short-term steroid treatment for goitrous ATD-treated Graves' patients appears promising in achieving goiter reduction or remission.

Key words: Graves' disease, Antithyroid drug (ATD) treatment, Vascular endothelial growth factor and its receptor (VEGF & flt), Steroid effect, Goiter

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GRAVES' disease is now considered to be an autoimmune disease causatively related with TSH receptor antibodies (TRAb) [1–3]. Until now, however, no effective treatment for the causative autoimmune mechanism has been developed. Three major classical means of treatment, antithyroid drug (ATD), surgery and radioiodide, are commonly used. Among these, ATD treatment is the most common choice in treating Graves'

patients in Japan [4, 5]. Unlike the opinions of other Thyroid Associations [6–8], Japanese thyroidologists prefer ATD, and they do not usually apply a uniform treatment protocol but treat patients for a long period of time until clinical remission is achieved [5]. The major criteria of remission are the disappearance of TRAb, achievement of euthyroidism including normalization of serum TSH, T₃ suppressibility, and reduction in goiter size. Reduction of goiter size has gained much attention for many years as an important indicator of remission [9–11].

Some growth stimulating factors, other than TSH or TRAb, have been considered to play significant roles in goiter formation [12–16], and recently

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Correspondence to: Dr. Toru MORI, Department of Laboratory Medicine, Kyoto University School of Medicine, 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto 606-01, Japan

several potential factors were demonstrated [17–19]. Even at the time of partial thyroidectomy in ATD-treated euthyroid Graves' patients, very rich vascularity with markedly large vessels can be seen, so that expressions of vascular endothelial growth factor (VEGF) and its receptor (flt) mRNAs in the thyroid tissue demonstrated by Sato *et al.* [19] are significant.

In this regard, and in order to reduce goiter size and to further facilitate clinical remission, we considered steroid to be a useful drug to suppress the effects of the VEGF-flt system. This was recently confirmed by Yamazaki *et al.* [20] through *in vitro* studies. In our study, we present the findings of a short-term steroid treatment in goitrous Graves' patients even after long ATD treatment and maintained euthyroidism. Although the number of patients studied was limited, this trial was quite effective.

Materials and Methods

Patients

Five Graves' patients were enrolled in the study. They were all females, 19 to 53 years old, and were treated with ATD for more than 25 months, including partial combination of ATD and l-thyroxine (T₄). The criteria of selection were as follows: 1) maintained in euthyroid states by ATD for at least 6 months, 2) negative or weakly positive for thyrotropin-binding inhibitor immunoglobulin (TBII), 3) T₃ unsuppressive, and 4) transverse diameter of the goiter was greater than 4.0 cm by palpation. They had no hyperglycemia or glycosuria and had normal HbA_{1c} values.

Study protocol

After receiving informed consent, 1.5 mg (1 mg in the morning and 0.5 mg after lunch) of betamethazone (Rinderon, Shionogi, Osaka) was given with the maintenance dose of ATD. After 2 weeks, the dose was reduced to 1 mg (0.5 mg × 2) and further to 0.5 mg (0.5 mg × 1) for 4 weeks, and then a 0.25 mg per day dose was administered for another month. The series was terminated for 3 months, and the patients were further treated with ATD only and observed for at least 3 months.

Measurements

Free T₄ (Ortho-diagnostic, Tokyo), T₃ (Dinabot, Tokyo), sensitive 2nd-generation TSH (Hoechst-Japan, Tokyo) and TBII (Cosmic Corp. Tokyo) were measured serially with commercially available radioassay kits. Goiter size was consistently measured only by T. M. with a scaler at the time of palpation. Capillary pulsation was also carefully palpated over the enlarged thyroid. T₃ suppression was tested by measuring ^{99m}Tc pertechnetate uptake before and after per os T₃ doses of 25 µg × 3 per day for a week. Positive suppression was defined when the post-T₃ uptake value was lower than half of the pre-T₃ value and also lower than 1%.

Thyroid stimulating antibody, anti-thyroglobulin antibody, anti-thyroid microsomal antibody and anti-thyroid peroxidase antibody were not measured serially before, during or after this study.

Results

Table 1 summarizes the clinical data of these 5 patients studied during the control observation period of 6 months. They took 5 to 7.5 mg of methimazole (MMI). Their fT₄ (0.96–1.58 ng/100 ml) and total T₃ levels remained within the normal range, and TSH was also detectable (0.7–3.4 µU/ml). TBII was negative in 3 cases and weakly positive in cases 4 and 5. Their goiter sizes fluctuated significantly but generally remained larger than 4.0 cm in diameter, and despite euthyroid states with negative or weakly positive TBII, they did not show significant reductions during the 6-month observation period. In most cases, capillary pulsation or thrill of the thyroid gland could be felt by palpation.

Table 2 shows changes in their thyroid states before, during and after the steroid treatment, and Fig. 1 shows those in goiter size. Immediately after the steroid administration, reductions in goiter size exceeding 0.7 cm were seen in all patients studied. These were partly reversed by the decrease in the steroid dosage, but continuous goiter size reductions were observed in 3 cases even 3 months after the cessation of steroid treatment. The other 2 cases showed some regrowth, much smaller than the pre-treatment levels.

As for the thyroid functions, 12 to 45 ng/100 ml

decreases in serum T₃ concentrations were observed 3 months after the initiation of steroid treatment, but all these decreases were partly reversed after 3 months. Similarly, 0.1 to 1.9 μ U/ml decreases in serum TSH concentrations were seen but also reversed afterwards. Free T₄ concentrations did not show any unidirectional changes, and final TBII activities were all negative, including the 2 cases with weakly positive values before the study.

Figure 2 shows the clinical course of case No.5 before, during and after the short-term steroid medication. This 19-y.o. girl was first diagnosed with Graves' disease in September, 1993. Conventional doses of MMI lowered her thyroid hormone and TBII levels, and in November, 1994 she was euthyroid with a TBII level of 17.1%, but her goiter size did not further reduce or enlarge. Steroid medication was initiated in October, 1995. This brought her apparent

reduction in goiter size, and thyroid states were kept within normal ranges. Even after the cessation of steroid treatment, her goiter did not grow, and TBII levels became normal. In February, 1996 a positive result of the T₃ suppression test with ^{99m}Tc-pertechnetate was obtained (4.5 $\rightarrow$ 0.8%). She has been followed up without ATD since February, 1996, and no signs of recurrence or increase in TBII were seen by October, 1996.

Finally, cases No. 4 and 5 were diagnosed in remission by the positive T₃ suppressibility of ^{99m}Tc-pertechnetate uptake. On the other hand, case No. 1 failed to be suppressed by T₃, and cases No. 2 and 3 have not undergone the T₃ suppression test.

No unfavorable adverse effects of steroid, including abnormal glucose metabolism, were encountered in any of these patients. The appearance of a moon face and/or slight increase in body weight were seen

Table 1. Clinical data of 5 Graves' patients studied during a 6 month-observation period prior to the study

Case	Age	Sex	Prev. Tx (months)	MMI dose (mg)	Goiter (cm)		fT ₄ (ng/100 ml)		T ₃ (ng/100 ml)		TSH (μ U/ml)		TBII (%)	
					max	min	max	min	max	min	max	min	max	min
1	45	F	62	5	5.7	5.2	1.19	0.92	113	90	3.4	1.8	0.9	-3.5
2	36	F	74	5	5.3	4.8	1.58	1.15	137	121	3.1	0.8	4.6	0.2
3	53	F	41	7.5	4.6	4.2	1.38	1.08	130	108	2.3	1.4	8.2	6
4	33	F	58	5	4.6	4.1	1.31	1.18	125	118	2.1	0.9	11.3	1.2
5	19	F	25	5	4.8	3.8	1.36	0.96	132	101	1.1	0.7	19	15.5

Prev. Tx: duration of previous MMI treatment in months before the study. MMI dose: maintenance daily dose of MMI during the study including observation period. For each parameter, at least 3 determinations were performed, and the maximal and minimal values are shown. Shortly before the entry in this study, all of these patients had been T₃ unsuppressive (data not shown).

Table 2. Changes in the thyroid states before, during and after a short-term steroid treatment in 5 Graves' patients

Case	Goiter (cm)			fT ₄ (ng/100 ml)			T ₃ (ng/100 ml)			TSH (μ U/ml)			TBII (%)		
	0	3M	6M	0	3M	6M	0	3M	6M	0	3M	6M	0	3M	6M
1	5.7	4.0	4.6	0.92	0.95	1.21	90	78	100	3.4	1.5	2.4	-3.5	5.4	3.6
		(4.0) ^a	(-1.1) ^b					(-12) ^c			(-1.9) ^d				
2	4.8	4.6	4.6	1.15	1.31	1.2	137	103	123	0.8	0.7	2.4	4.6	7.3	3.3
		(4.0)	(-0.2)					(-34)			(-0.1)				
3	4.4	3.8	3.8	1.23	1.61	1.25	130	85	112	1.4	0.6	1.8	6.0	-0.5	2.8
		(3.6)	(-0.6)					(-45)			(-0.8)				
4	4.3	3.8	3.5	1.31	1.51	0.98	118	91	98	2.1	1.3	3.0	11.3	-2.4	7.1
		(3.5)	(-0.8)					(-27)			(-0.8)				
5	4.2	3.6	3.3	0.96	1.22	1.1	101	85	105	1.1	0.4	1.1	15.5	12.8	7.5
		(3.5)	(-0.9)					(-16)			(-0.7)				

a: Numbers in parentheses in this row show the minimal values observed during steroid administration.

b, c, d: Numbers in parentheses in these rows indicate differences from those in the pre-treatment stage.

Fig. 1. Alterations in goiter size before, during and after a short-term steroid treatment in 5 ATD treated Graves' patients studied. After the observation period for 6 months under the maintenance dose of MMI, 1.5 mg daily dose of betamethazone together with MMI was given at 0, and the dosage was gradually tapered to 0 mg for 3 months. Then the patients were observed for another 3 months under the same dosage of MMI only. Each symbol indicates individual cases presented; square, Case 1; diamond, Case 2; triangle, Case 3; inverted triangle, Case 4; circle, Case 5, respectively.

Fig. 2. Clinical course of a 19 y.o. Graves' patient (Case 5) who showed remarkable reduction in goiter size and also entered remission after a short-term steroid treatment. A positive result of T₃ suppression test was obtained on January, 1996, and then methimazole medication was discontinued.

in 3 of these patients in the early phase of steroid treatment, but these diminished shortly after the reduction of the steroid dosage.

Discussion

ATD is the first-choice treatment for most Graves' patients, especially in Japan [4, 5]. Indeed, ATD is quite effective in ameliorating hyperthyroidism in almost all patients, but it is still uncertain when ATD treatment should be terminated or how clinical remission should be determined. The disappearance of TRAb, positive T_3 suppression test, achievement and maintenance of euthyroidism by a minimal ATD dosage, or increase in the serum TSH concentration are major indicators of clinical remission of Graves' disease [5]. Nevertheless, even with a combination of all these indicators, one cannot confidently predict the clinical remission of a patient.

Reduction in goiter size should be added as another criterion for clinical remission of Graves' disease under ATD treatment. This has been pointed out for many years [9–11], and Japanese thyroidologists have taken this to be an important indicator [5]. Reduction in goiter size during ATD treatment can vary from patient to patient, and some growth-stimulatory mechanisms irrespective of TSH may be involved. The presence of thyroid cell growth-stimulating immunoglobulin has been demonstrated [12], but later studies, including ours, showed that the growth stimulatory activity of Graves' IgG was mostly related to TSAb activity [13–15]. Various growth factors and cytokines have been studied extensively in this regard, and some potential factors have been indicated [16–19]. Among these, we considered the VEGF-flt mechanism [21, 22] significant, because hypervascularity or capillary pulsation of an enlarged gland is a common feature of Graves' patients with a large goiter even after long-term ATD treatment [23, 24]. To eradicate these assumed VEGF-flt effects, a short-term and moderate-dose steroid treatment was chosen for a clinical trial. Indeed, Yamazaki *et al.* [20] demonstrated *in vitro* evidence of steroid's effectiveness on reducing the expression of VEGF mRNA in cultured Graves' thyroid cells. Though steroid has immunosuppressive effects and Graves' disease is an autoimmune disease, therapeutic effects

of steroid on Graves' hyperthyroidism cannot be expected, but large-dose applications may induce some immunological effects and may also induce some adverse effects, such as diabetes mellitus.

Steroid medication immediately induced significant goiter reduction in all 5 patients in association with a decrease in or the disappearance of goiter capillary pulsation. Decreasing the steroid dosage partly reversed the observed reductions, and in 2 patients, goiter regrowth was observed after the cessation of steroid treatment. We did not apply more reliable ultrasonographic measurement of the goiter size, but the observed changes appear to be significant enough. Increased or longer-term dosages may have been more effective, but this protocol seemed suitable to avoid the unfavorable adverse effects of steroid seen in ambulatory cases. As expected, this amount of steroid induced decreases in serum T_3 and TSH concentrations but not in fT_4 . As for immunosuppressive effects, TBII levels in these patients were negative or weakly positive, and we did not measure other thyroid autoantibodies serially. In 2 patients (Cases 4 and 5), TBII became negative, but this may also be the result of the reduction in goiter size or vascularity in the goiter. In patients with Hashimoto thyroiditis, steroid medication at such a dosage may reduce the goiter size. Besides the inhibition of the VEGF/flt mechanism, the observed steroid effects may also involve the immunosuppressive mechanism.

Although this is a preliminary study, and the number of patients studied was quite limited, the findings obtained with this short-term steroid treatment may give some new insights into the treatment of long-term Graves' patients under ATD, who are kept euthyroid by ATD, whose TBII are not markedly elevated, but who have considerable goiter size and T_3 unsuppressiveness.

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