High-Dose Intravenous Steroid Pulse Therapy in Thyroid-Associated Ophthalmopathy

TETSUYA TAGAMI, KIYOSHI TANAKA, HIDEO SUGAWA*, HIROTOSHI NAKAMURA**, YOJI MIYOSHI, TORU MORI*, AND KAZUWA NAKAO

Departments of Medicine and Clinical Science, and

**Laboratory Medicine, Kyoto University Graduate School of Medicine, Kyoto 606-01, and*

***Second Division, Department of Internal Medicine, Hamamatsu Medical School, Hamamatsu 431-31, Japan*

Abstract. To evaluate the efficacy of high-dose intravenous steroid pulse followed by oral steroids in the treatment of thyroid-associated ophthalmopathy, we performed clinical assessment and measurement of retroorbital muscle enlargement in 27 patients before and after the therapy, and followed them up longitudinally. The mean duration of follow up is (mean $\pm$ SD) 29.8 ± 23.8 months (range 4–92). Diplopia disappeared in 10 patients and ameliorated in 11 patients. The degree of proptosis decreased in 15 patients and the fall in visual acuity improved in a third of the patients. The total ophthalmopathy index (OI) decreased from 7.0 ± 1.9 to 3.0 ± 1.5 . The extraocular muscle enlargement (EME), expressed as the maximal ratio of extraocular muscle thickness to the diameter of the optic nerve, decreased from 2.33 ± 0.56 to 1.27 ± 0.26 . No major side effects were found in any patient. The improvement in the eye disease was found immediately after the pulse therapy, prior to the start of the following therapy by oral steroids and/or orbital irradiation. Both of OI and EME decreased with time after the therapy and did not get worse after withdrawing oral steroids. The efficacy of the therapy evaluated by degrees of improvement in OI and in EME was significantly greater in females than in males. Although there was a significant positive correlation between initial OI and EME values and initial TBII and TSAb activities, a significant correlation was seen only between the degrees of improvement in EME and changes in TBII activity due to the therapy. The duration of eye disease, thyroid status, treatment with anti-thyroid drug, smoking and experience of previous treatment did not affect the efficacy of the present therapy. We conclude that high-dose intravenous steroid pulse therapy is effective and safe for thyroid-associated ophthalmopathy.

Key words: Intravenous steroid, Pulse therapy, Thyroid, Ophthalmopathy

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THYROID-associated ophthalmopathy (TAO) is a progressive eye disorder ranging from disfiguring proptosis and diplopia to sight loss and is typically associated with Graves' hyperthyroidism. Although it also occurs, occasionally, in patients without hyperthyroidism, they often show some

abnormalities in thyroid function and immunology [1]. TAO seems to be caused by an autoimmune mechanism related to the thyroid [2–4]. Various immunosuppressive therapies have been reported, including systemic steroids [5], retrobulbar steroids [6], azathioprine [7], cyclophosphamide [8], cyclosporine [9, 10], plasmapheresis [11, 12], high-dose immunoglobulin [13] and combinations thereof [14, 15]. Although high-dose systemic corticosteroids, e. g. prednisolone 80–100 mg daily, have been used with some success, there is a high tendency to relapse as the steroid doses are reduced and often maintenance levels of 30 mg per

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Correspondence to: Dr. Tetsuya TAGAMI, Endocrinology, Metabolism and Molecular Medicine, Tarry 15, Northwestern University Medical School, 303E. Chicago Ave., Chicago, IL 60611, USA

day or more are needed, which leads an increase in the frequency and severity of adverse effects [16]. Intravenous methylprednisolone, which should be used only with strict medical monitoring and hospitalization, is more effective and its adverse effects are less [17–20]. Radiotherapy has re-emerged as another useful form of treatment, e. g. megavoltage, highly collimated beams from a linear accelerator are lymphocytotoxic [21, 22].

In the present study, we investigated the effects of intravenous high-dose methylprednisolone therapy with or without orbital irradiation in patients with TAO.

Patients and Methods

Patients

Twenty-seven patients with TAO (12 men and 15 women), aged 33–66 years (mean 46.6), were studied. Table 1 gives clinical manifestations of the patients at the start of the study. Seventeen patients had hyperthyroid Graves' disease. The remaining 10 patients had euthyroid Graves' ophthalmopathy, the diagnosis of which was based on Graves' ophthalmopathy in clinically euthyroid subjects with normal serum free T4 and T3 concentrations and without any previous history of an overt dysthyroid state. All the patients presented with diplopia and eight of the patients had received some previous immunosuppressive treatment, as shown in Table 1, which resulted in a transient improvement but there was recurrence of their ophthalmopathy. Patient No. 10 (10A) was treated with intravenous methylprednisolone followed by orbital irradiation but he stopped oral prednisolone by himself and his ophthalmopathy relapsed. The same patient (No. 10B) was treated again with intravenous methylprednisolone. Patient No. 12 underwent thyroidectomy 12 years before the present therapy for her ophthalmopathy and patients Nos. 2 and 6 after therapy for Graves' hyperthyroidism. No other patients had been treated previously with radioactive iodine or thyroidectomy. The mean duration of the eye disease was 29.1 ± 48.5 months (range 3–240) and the mean duration of stability of the ophthalmopathy was 4.2 ± 2.0 months (range 1–10). The mean duration of hyperthyroidism in the hyperthyroid

group was 39.5 ± 65.7 months (range 1–276). Whether each patient was a smoker (>10 cigarettes/day) or a non-smoker is indicated. All the patients had some disorders of the thyroid, including thyroglobulin or microsomal antibodies, TSH receptor antibodies, thyroid-stimulating antibodies, abnormality of the T3-suppression test or the TRH test, and had various degrees of goiter. Hyperthyroid patients were treated with antithyroid drugs (methimazole, MMI; or propylthiouracil, PTU) and hypothyroid patient No. 12 was treated with levothyroxine (L-T4) after thyroidectomy. They were almost all euthyroid at the time when treatment for their ophthalmopathy was started.

Evaluation of thyroid function and antithyroid antibodies

Serum free thyroxine (T4) and total triiodothyronine (T3) were measured directly by RIA (free T4, Nippon Kodak Diagnostics, Tokyo, Japan; total T3, Dainabot, Tokyo, Japan). The serum TSH level was determined by a sensitive IRMA (Hoechst Japan, Tokyo, Japan). Titers of antibodies to thyroglobulin and thyroid microsomal antigen were determined by the passive agglutination technique (Fujizoki Inc., Tokyo, Japan). TSH-binding inhibitor immunoglobulins (TBII) were assayed with a commercially available kit (Cosmic Corp., Tokyo, Japan) with minor modifications [23]. Thyroid-stimulating antibodies (TSAb) were assayed by a modified method developed by Mori *et al.* [24, 25]. Cyclic AMP, produced by FRTL-5 thyroid cells exposed to immunoglobulin fractions, was measured.

The T3-suppression test was performed by counting the thyroidal ^{99m}Tc uptake at 30 min after intravenous injection of ^{99m}Tc pertechnetate, before and after oral administration of $75 \mu\text{g/day}$ of T3 for a week. In 2 patients (cases Nos. 4 and 5), ^{123}I thyroid uptake was determined at 24 h after oral administration of ^{123}I . The TRH test was performed in all the patients with euthyroid Graves' ophthalmopathy by measuring serum TSH concentrations before and 30, 60 and 120 min after $500 \mu\text{g}$ intravenous TRH injection. The time of peak TSH levels as shown in Table 2 was at 30 min after iv in all the patients tested.

Table 1. Clinical manifestations of patients with thyroid-associated ophthalmopathy

Patient No.	Age (yr)	Sex (M/F)	Duration of Eye disease (mo)	Duration of hyperthyroid (mo)	Previous treatment ^a	Number of pulses	Radiation (Gy)	Post treatment	Smoking
Hyperthyroid Group									
1	41	F	13	16	–	3	20	–	No
2	33	F	60	276	20Gy	4	–	Tx	No
3	47	F	6	5	–	3	–	–	No
4	46	F	30	16	–	2	–	–	No
5	40	F	8	9	–	3	20	–	Yes
6	42	M	10	60	PDN (100)	3	–	Tx	Yes
7	52	M	6	5	–	3	–	–	Yes
8	49	F	6	2	–	3	20	–	No
9	46	M	80	70	DMS(RB)+PDN(60)	3	20	–	Yes
10A	37	M	10	6	PDN(80)	3	20	–	Yes
10B	38	M	20	8	3 pulses+20Gy	3	–	–	Yes
11	50	F	4	5	–	3	–	–	No
12	66	F	240	84	Tx	2	–	–	Yes
13	50	F	88	88	PDN(30)	2	–	–	No
14	46	F	10	22	–	4	20	–	Yes
15	43	F	9	18	–	3	–	–	No
16	43	F	10	1	–	3	–	–	No
17	57	M	3	20	–	3	20	–	Yes
Euthyroid Group									
18	47	F	6	–	–	3	–	–	No
19	38	F	22	–	–	2	20	–	No
20	57	M	18	–	–	2	–	–	No
21	65	M	20	–	PDN (45)	3	–	–	Yes
22	42	M	7	–	–	3	–	–	No
23	52	M	6	–	PDN(?)	3	20	–	Yes
24	49	M	7	–	PDN(30)	3	20	–	Yes
25	43	F	3	–	–	3	20	–	Yes
26	39	M	103	–	–	3	–	–	Yes
27	46	M	11	–	–	3	20	–	Yes

^a20Gy, orbital radiotherapy; PDN(–), oral prednisolone (mg/day); DMS (RB), dexamethasone (retrobulbar); Tx, thyroidectomy.

High-dose intravenous steroid pulse therapy

After informed consent was obtained, methylprednisolone sodium succinate (1 g) was infused iv over 120 min daily for 3 successive days. This course was repeated at intervals of 1 week, until ophthalmopathy showed great improvement (up to 4 times). After the series of intravenous high-dose methylprednisolone therapy was finished, oral prednisolone treatment was started with an initial dose of 40–50 mg/day. It was then gradually tapered and withdrawn within 3–12 months. Evaluations of OI, EME, TBII and TSAb after the pulse therapy were performed one month after the start of pulses.

Radiotherapy procedure

After the pulse therapy, its efficacy in each case was discussed by the endocrinologist, ophthalmologist and radiologist and the indication for radiotherapy was decided. Orbital radiotherapy was also begun in 12 cases, within 2 weeks after the series of pulse therapies were finished. Irradiation to the orbit of the side(s), in which the swelling of extraocular muscle(s) was found by CT or MR imaging, was performed with an X-ray beam with an energy of 10 MeV generated by a linear accelerator [26]. Ten daily doses of 200 cGy to each eye were given in 2 weeks for a cumulative dose of 20 Gy. In cases where both eyes should be

Table 2. Individual responses to intravenous high-dose methylprednisolone followed by orbital irradiation or not

Patient No.	Ophthalmopathy index			Proptosis (rt/lt:mm)		Duration of follow up (mo)	Clinical assessment
	Initial	Final	Changes	Initial	Final		
Hyperthyroid Group							
1	8 (S 3 P 2 E 2 C 1 Si 0)	5 (S 1 P 1 E 2 C 1 Si 0)	−3	21/21	18/16	92	Good
2	10 (S 3 P 3 E 2 C 2 Si 0)	5 (S 0 P 3 E 1 C 1 Si 0)	−5	30/33	25/26	87	Good
3	7 (S 3 P 1 E 2 C 1 Si 0)	4 (S 1 P 1 E 1 C 1 Si 0)	−3	19/18	17/18	25	Good
4	6 (S 2 P 2 E 2 C 0 Si 0)	2 (S 0 P 2 E 0 C 0 Si 0)	−4	22/21	21/20	54	Good
5	9 (S 3 P 3 E 2 C 1 Si 0)	3 (S 0 P 1 E 1 C 1 Si 0)	−6	21/23	17/18.5	45	Excellent
6	6 (S 2 P 2 E 2 C 0 Si 0)	1 (S 0 P 1 E 0 C 0 Si 0)	−5	22/20	18/17	59	Excellent
7	4 (S 1 P 1 E 2 C 0 Si 0)	2 (S 0 P 1 E 1 C 0 Si 0)	−2	19/18	17/18	43	Good
8	7 (S 3 P 2 E 2 C 0 Si 0)	2 (S 0 P 1 E 1 C 0 Si 0)	−5	20/22	19/19.5	42	Excellent
9	10 (S 3 P 3 E 2 C 1 Si 1)	6 (S 1 P 3 E 2 C 0 Si 0)	−4	24/26	22/23	37	Good
10A	10 (S 2 P 3 E 2 C 1 Si 2)	relapse ^a		24/24	relapse	9	
10B	9 (S 3 P 2 E 1 C 1 Si 2)	3 (S 0 P 1 E 0 C 0 Si 2)	−6	21/20	19/19	20	Excellent
11	7 (S 2 P 2 E 2 C 1 Si 0)	2 (S 0 P 1 E 0 C 1 Si 0)	−5	21/20	18/17	20	Excellent
12	9 (S 3 P 3 E 2 C 1 Si 0)	3 (S 0 P 3 E 0 C 0 Si 0)	−6	26/26	24/24	14	Excellent
13	7 (S 2 P 2 E 2 C 1 Si 0)	1 (S 0 P 1 E 0 C 0 Si 0)	−6	22/20	19/18	14	Excellent
14	6 (S 2 P 1 E 2 C 1 Si 0)	3 (S 0 P 0 E 2 C 1 Si 0)	−3	16/15	15/15	11	Good
15	3 (S 1 P 1 E 1 C 0 Si 0)	1 (S 0 P 1 E 0 C 0 Si 0)	−2	17/17	16/15	11	Good
16	6 (S 2 P 1 E 2 C 1 Si 0)	2 (S 0 P 0 E 1 C 1 Si 0)	−4	17/12	15/12	8	Good
17	7 (S 3 P 2 E 2 C 0 Si 0)	4 (S 1 P 1 E 2 C 0 Si 0)	−3	16/20	17/18	7	Good
Euthyroid Group							
18	7 (S 2 P 2 E 2 C 1 Si 0)	2 (S 0 P 1 E 1 C 0 Si 0)	−5	20/18	17/16	30	Excellent
19	7 (S 2 P 2 E 2 C 1 Si 0)	2 (S 1 P 1 E 0 C 0 Si 0)	−5	19/22	17/15	68	Excellent
20	7 (S 2 P 3 E 2 C 0 Si 0)	4 (S 0 P 3 E 1 C 0 Si 0)	−3	19/24	18/23	4	Good
21	7 (S 2 P 2 E 2 C 1 Si 0)	4 (S 0 P 2 E 2 C 0 Si 0)	−3	20/21	20/20	18	Good
22	7 (S 2 P 3 E 2 C 0 Si 0)	4 (S 0 P 3 E 1 C 0 Si 0)	−3	25/24	25/26	14	Good
23	5 (S 1 P 2 E 2 C 0 Si 0)	3 (S 0 P 2 E 1 C 0 Si 0)	−2	21/21	20/19	15	Good
24	7 (S 3 P 2 E 2 C 0 Si 0)	2 (S 0 P 1 E 1 C 0 Si 0)	−5	22/20	18/17	42	Excellent
25	3 (S 0 P 1 E 2 C 0 Si 0)	0 (S 0 P 0 E 0 C 0 Si 0)	−3	16/19	14/15	29	Excellent
26	5 (S 2 P 2 E 1 C 0 Si 0)	2 (S 0 P 2 E 0 C 0 Si 0)	−3	20/20	20/19	12	Good
27	10 (S 3 P 3 E 2 C 1 Si 1)	6 (S 1 P 1 E 2 C 1 Si 1)	−4	24/19	19/19	5	Good

^aThis patient stopped oral prednisolone by himself and relapsed. He received an additional pulse therapy, and improved and remains improved. S, soft tissue; P, proptosis; E, eye muscle impairment; C, corneal involvement; Si, degree of sight loss.

treated, 100 cGy to each eye with a total dose of 200 cGy daily was given. Evaluations of OI, EME, TBII and TSAb after the radiotherapy were performed 2 months after the start of pulses.

Ophthalmopathy index (OI)

The severity of ocular involvement was evaluated by physical examination by Hertel exophthalmometry, extraocular-muscle function tests with a Hess chart, retinoscopy, testing of the visual field and acuity, tonometry, and corneal examination before and after the therapy. The patients were evaluated not only by two or more

of the same endocrinologists but also by the same ophthalmologist during the study. The examining physicians were aware of the treatment methods used. The ophthalmopathy index (OI) [27] was calculated on the basis of the American Thyroid Association Classification of Graves' eye disease [28], with minor modifications. The signs and symptoms of each patient's ophthalmopathy were evaluated with respect to five specific parameters: soft tissue (S), proptosis (P), eye muscle impairment (E), corneal involvement (C), and degree of sight loss (Si). Each parameter was given a score of 0–3. The score for proptosis was modified as follows, since exophthalmos in Japanese patients

is less prominent than in Caucasians [28]: <16 mm=0, 16–20 mm=1, 20–23 mm=2, >23 mm=3. The degree of diplopia was assessed on the basis of the results not only of extraocular-muscle function tests but also of the Hess chart test. The results of treatment were also assessed with the classification of Donaldson *et al.* [27] by an endocrinologist. The mean time lapse between the start of the therapy and the final assessment of OI and clinical responses after the therapy was 29.8 ± 23.8 months (range 4–92).

Evaluations of the orbits by computerized tomography (CT) or magnetic resonance (MR) imaging

Orbits were scanned by high resolution CT or with a superconducting MR unit in the axial and coronal planes with slices made at 3 mm. The thicknesses of superior, medial, inferior, and lateral rectus muscles were measured at the site of their enlargement bilaterally before and after the therapy. The EME was expressed as the ratio of thickness of the most enlarged eye muscle to the diameter of the optic nerve to exclude individual variations [29, 30]. The mean time lapse between imaging before the therapy and the final imaging after the therapy was 20.3 ± 21.3 months (range 6–86).

Statistical analysis

Data were analyzed for statistical significance by analysis of variance in combination with Student's unpaired and paired *t*-test and by correlation coefficient to evaluate the correlation between two series of data. When the effects of treatment on OI and on EME in the patients split by various parameters were examined, the time lapse between initial and final evaluations in each group were not significantly different.

Results

Changes in mean values for total OI and its individual components are shown in Fig. 1. Total OI decreased significantly immediately after the pulse therapy (before the following therapy by oral steroids and/or orbital irradiation) from 6.7 ± 1.7

to 3.9 ± 1.4 ($P < 0.0001$) in patients treated with pulses alone and from 7.4 ± 2.1 to 5.3 ± 2.0 ($P < 0.0001$) in those treated with pulses plus orbital irradiation. Soft tissue involvement and exophthalmos also decreased significantly immediately after pulses, and the former kept pace with the total OI but the latter did not necessarily. The pulse therapy divided the patients into two groups, e.g. very effective and not effective on diplopia. The patients whose diplopia showed little improvement were then treated with orbital irradiation.

The clinical assessments of the effect of pulse therapy with or without orbital irradiation for TAO are shown in Table 2. Soft tissue changes at the end of the follow-up period showed regression or improvement in all patients. The degree of proptosis decreased in 10/17 patients in the hyperthyroid (HR) group and in 5/10 of those in the euthyroid (EU) group. Diplopia disappeared in 7 patients in the HR group and in 3 in the EU group, and ameliorated in 6 patients in the HR group and 5 in the EU group. Corneal involvement was improved in 5/12 in the HR group and in 3/4 of those in the EU group. The fall in visual acuity, due to optic nerve involvement found by the retinoscopic examination, was observed in 3 patients before the therapy and the acuity improved from 0.7 to 1.2 in case No. 9 with regression of compressive optic nerve neuropathy.

Figure 2A shows individual changes in extraocular muscle enlargement (EME), expressed as the maximal ratio of extraocular muscle thickness to the diameter of the optic nerve. The EME decreased with the time after the therapy (initial 2.33 ± 0.56 ; after therapy (<6 months) 1.67 ± 0.42 , $P < 0.0001$ vs. initial; final (>6 months) 1.27 ± 0.26 , $P < 0.0001$ vs. initial, $P = 0.0002$ vs. after therapy) (Table 3). The individual changes in TBII activity and those in TSAb activity are shown in Figs. 2B and 2C, respectively. There were significant correlations between initial OI values and initial TBII activities ($R = 0.406$, $P = 0.0322$), initial OI values and initial TSAb activities ($R = 0.573$, $P = 0.0014$), and initial EME values and initial TBII activities ($R = 0.415$, $P = 0.0351$). Significant correlations were seen between the degrees of improvement in OI and those in EME after the therapy ($R = 0.413$, $P = 0.0361$) and between the latter and changes in TBII activity due to the therapy [(activity before treatment – activity after treatment)/(activity before treatment)]

Fig. 1. Mean serial changes in values for the ophthalmopathy index and its individual components. Results shown are the mean $\pm$ SD at each time point indicated, in the patients treated with irradiation (○—○) and without irradiation (●....●) * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ vs. initial, by paired t -test.

($R=0.491$, $P=0.0204$). The initial OI and the initial EME did not necessarily correlate.

We examined the effects of treatment on OI and on EME in the patients split by various parameters (Table 3). The mean initial OI value was significantly higher in patients with positive TBII than that with negative TBII ($P < 0.05$) reflecting the correlation between OI and TBII as mentioned above. The mean initial OI value in patients who

received previous immunosuppressive treatment, most of which was oral prednisolone, was also higher than that in remaining patients, but there was no difference between their final OI values after the therapy. A significant difference in the mean initial EME value was found between the patients who were treated with anti-thyroid drug during the present therapy to their hyperthyroidism and the patients who were not ($P < 0.05$), but

Fig. 2. Individual changes in extraocular muscle enlargement (EME) (A), TBII activity (B) and TSAb activity (C) in the patients treated with methylprednisolone pulses. EME is expressed as the maximal ratio of extraocular muscle thickness to the diameter of the optic nerve evaluated by CT scan or MR imaging., patients treated with steroid pulses alone; —, patients treated with pulses followed by orbital irradiation. POST P, after steroid pulse therapy (one month after the start of pulses); POST R, after orbital irradiation (two months after the start of pulses).

not between the hyperthyroid and euthyroid groups. The mean initial EME value in female patients was significantly lower than that in male patients ($P < 0.05$), and that in non-smokers among the patients was also lower than that in smokers ($P < 0.05$). Interestingly, however, there was no difference between smokers and non-smokers in the efficacy of the present therapy, whereas the degrees of improvement both in OI and in EME were significantly higher in females than in males

($P < 0.05$ and $P < 0.01$, respectively). There was not a significant correlation between the duration of eye disease and the efficacy of the therapy evaluated by OI or EME. Finally there was a positive correlation between initial values and absolute decompression in EME (initial value – final value) due to the present therapy ($R = 0.792$, $P = 0.0022$), e.g. the present therapy had a sufficient effect on retroocular muscles with severe swelling as well on those with mild swelling.

Minor side effects were found in some patients, including viral pneumonia in case No. 2, mild gastritis in case No. 4, hypercholesterolemia (up to 300 mg/dL) in case No. 8, and irritation or anxiety in cases No. 3, 12, 19, 20 and 25. Each symptom or sign was controlled with appropriate medicines and disappeared with the completion of the pulse therapy. Although some patients had combined diseases, such as impaired glucose tolerance (cases No. 2, 10, 12, 13, 17, 20, 24 and 25) or a history of tuberculosis (case No. 21), no aggravation of diabetes mellitus or reactivation of tuberculosis was found with the administration of insulin or anti-tuberculous drugs during the pulse therapy. No other major side effects, including the occurrence of bone fracture, gastrointestinal bleeding (with the administration of H₂-blocker) and fall in serum potassium, were found in any of the patients.

Discussion

Various medical therapeutic trials have been performed for TAO based on the assumption that TAO is an autoimmune disease [2–4]. The results are, however, often controversial and not satisfactory, especially in the case of diplopia or proptosis [31–33]. Although the most effective of the drugs used for immune suppression seem to be steroids, high oral dosage is necessary for a long time, and causes serious adverse effects [16]. Intravenous high-dose steroid pulse therapy is reported to be more effective and adverse effects are less [18]. In the present study we investigated the effects of the pulse therapy in 17 patients with hyperthyroid Graves' ophthalmopathy and in 10 patients with euthyroid Graves' ophthalmopathy. The results were evaluated with the ophthalmopathy index, in the absence of other universally acceptable methods, and the thickness of the eye muscle detected

Table 3. Effects of treatment on ophthalmopathy index and extraocular muscle enlargement in the patients split by various parameters

	No. of patients	Ophthalmopathy index			Extraocular muscle thickness/Diameter of the optic nerve (EME)			
		Initial (I)	Final (F) ^a	Degree of improvement (I-F)/I×100(%)	Initial (I)	After therapy (<6 months)	Final (F) ^a (>6 months)	Degree of improvement ((I-1)-(F-1))/((I-1)×100%)
TOTAL	27	7.00 ± 1.91	2.96 ± 1.52	59.2 ± 16.1	2.33 ± 0.56	1.67 ± 0.42	1.27 ± 0.26	82.1 ± 15.6 (16) ^c
Hyperthyroid	17	7.28 ± 1.94	3.00 ± 1.49	59.7 ± 14.2	2.21 ± 0.51	1.69 ± 0.42	1.29 ± 0.30	82.0 ± 16.5 (11)
Euthyroid	10	6.50 ± 1.75	2.90 ± 1.58	58.3 ± 19.1	2.51 ± 0.60	1.64 ± 0.43	1.23 ± 0.15	82.2 ± 13.4 (5)
Male	12	7.23 ± 1.93	3.54 ± 1.50	51.8 ± 13.6*	2.60 ± 0.46*	1.82 ± 0.36*	1.49 ± 0.28*	66.9 ± 12.7 (5)**
Female	15	6.80 ± 1.87	2.47 ± 1.36	65.7 ± 15.3	2.09 ± 0.54	1.53 ± 0.43	1.17 ± 0.18	88.9 ± 11.4 (11)
Smoker	13	7.29 ± 2.22	3.14 ± 1.68	59.3 ± 17.1	2.58 ± 0.47*	1.86 ± 0.41*	1.35 ± 0.31	78.2 ± 16.6 (7)
Non-smoker	14	6.71 ± 1.48	2.79 ± 1.30	59.1 ± 15.1	2.07 ± 0.54	1.49 ± 0.36	1.21 ± 0.19	85.1 ± 14.1 (9)
ATA ^b positive	12	6.75 ± 2.24	3.08 ± 1.75	57.6 ± 19.1	2.26 ± 0.45	1.66 ± 0.35	1.27 ± 0.18	80.7 ± 14.6 (9)
ATA negative	15	7.19 ± 1.59	2.88 ± 1.32	60.4 ± 13.3	2.37 ± 0.62	1.68 ± 0.46	1.27 ± 0.33	83.8 ± 16.6 (7)
TBII positive	17	7.61 ± 1.77*	3.28 ± 1.63	58.4 ± 15.5	2.21 ± 0.50	1.67 ± 0.39	1.20 ± 0.19	84.8 ± 14.8 (5)
TBII negative	10	5.90 ± 1.64	2.40 ± 1.11	60.7 ± 17.2	2.51 ± 0.61	1.67 ± 0.47	1.44 ± 0.32	76.0 ± 15.7 (11)
Irradiation								
with	11	7.42 ± 2.06	3.42 ± 1.75	56.8 ± 18.5	2.44 ± 0.44	1.78 ± 0.40	1.20 ± 0.15	86.3 ± 11.0 (9)
without	16	6.69 ± 1.72	2.63 ± 1.22	61.0 ± 13.8	2.23 ± 0.64	1.59 ± 0.42	1.36 ± 0.33	76.6 ± 18.7 (7)
Anti-thyroid drug								
with	11	7.18 ± 1.95	3.00 ± 1.71	58.2 ± 16.5	1.99 ± 0.50*	1.56 ± 0.40	1.21 ± 0.21	85.3 ± 14.7 (7)
without	16	6.75 ± 1.55	2.94 ± 1.43	58.2 ± 16.5	2.49 ± 0.53	1.68 ± 0.40	1.30 ± 0.30	80.7 ± 16.3 (8)
Previous treatment								
with	7	8.25 ± 1.56*	3.38 ± 1.80	61.3 ± 16.8	2.09 ± 0.45	1.48 ± 0.25	1.06 ± 0.26	94.2 ± 26.0 (3)
without	20	6.50 ± 1.80	2.80 ± 1.36	58.4 ± 15.8	2.41 ± 0.58	1.74 ± 0.45	1.32 ± 0.26	79.3 ± 15.8 (13)

* $P < 0.05$, ** $P < 0.01$, by unpaired *t*-test. ^aThe time elapsed between initial and final evaluations in each group was not significantly different. ^bATA, antibody to thyroglobulin or thyroid microsomal antigen. ^cThe number of patients finally assessed by EME is given in parenthesis. Data are the mean ± SD.

by CT scan or MR imaging. All patients presented with diplopia and it improved in 21 patients (78%). The degree of proptosis decreased in 14 patients (52%) and the fall in visual acuity due to compressive optic nerve neuropathy improved in a third of patients. The improvement in eye disease was found immediately after the pulse therapy and subsequent oral prednisolone treatment consolidated the efficacy. None of the patients has shown any sign of relapse of their ophthalmopathy in a long follow-up. It is considered that the present therapy was more effective than others [14]. Although extraocular muscle dysfunction in particular has been considered to be refractory to other therapies

[5, 10, 27, 32], it is reported that 60% [18] or 75% [20] of patients showed a loss of diplopia with steroid pulse therapy. Orbital irradiation was combined in the latter study and with it we treated patients whose diplopia showed little improvement with pulses. Orbital irradiation may be helpful for diplopia, but since there was a relapsed patient who rapidly tapered off oral prednisolone by himself in the present study, we should taper it off very carefully to maintain the effect of pulse therapy. The duration of eye disease, thyroid status, treatment with anti-thyroid drugs, smoking and experience of previous treatment did not affect the efficacy of the present

therapy. It is reported that MMI treatment did not influence the course of TAO [34]. Recently, Perros *et al.* [35] published a paper about the natural history of TAO, and 64.4% of patients improved spontaneously, 22% did not change and 13.5% deteriorated. The patients on the present therapy were limited to those whose ophthalmopathy was stable for at least 3 months. Moreover, both OI and EME decreased immediately after the pulse therapy.

After elaborate pre-therapeutic examination and under close medical monitoring, no major side effects were found, e.g. aggravation of diabetes mellitus, reactivation of tuberculosis, gastrointestinal bleeding, fall in serum potassium and rapid deterioration of bone density in post-menopausal women. Since irritation or anxiety was found in 5 cases during the series of pulses, effects on mood and mental performance should be monitored carefully. Although there is not a control group of patients who only had oral steroids without intravenous steroid pulse in the present study, therapy with systemic steroids has been associated with serious side effects [10, 13, 22]. There were no severe side effects during pulses and oral steroids. Our results indicate the safety of steroid pulse therapy itself under close medical monitoring, and possibly pulses reduce the total dose of subsequently administered oral steroids.

There was a significant positive correlation between initial OI and EME values and initial TBII and TSAb activities. Several reports on a correlation between the severity of the eye disease and TSAb activity are controversial. Nishikawa *et al.* [30] reported that the level of the stimulating activity in Graves' patients with ophthalmopathy showed a significant positive correlation with the ratios of swelling of the eye muscles. On the other hand, no correlation was observed between the TBII activity and muscle swelling. Some other authors [36, 37] failed to show a positive correlation between the severity of the eye disease and TSAb activity. The treatment of hyperthyroidism with anti-thyroid drugs or of ophthalmopathy with steroids appear to reduce TBII and TSAb activities in a nonspecific manner. In the present study, there was a case (No. 17) whose eye disease developed rapidly even though his TBII and TSAb activities decreased before the pulse therapy. He was diagnosed as having Graves' hyperthyroidism without

ophthalmopathy, and treatment with MMI was started. TBII and TSAb activities decreased gradually but severe ophthalmopathy newly appeared in 9 months after the start of MMI. Both TBII and TSAb activities at that time were suppressed. An initial high titer of TBII or TSAb activity may have strongly stimulated his retroorbital tissue. If this is not a special case, we should evaluate the role of TSH receptor autoantibodies in ophthalmopathy in all cases, using the activity showing a high titer instead of that immediately before the start of the pulse therapy. Rotella *et al.* [37] reported that immunoglobulin G (IgG) preparations from 17 of 20 hyperthyroid patients with Graves' ophthalmopathy stimulated collagen biosynthesis in human fibroblasts, as measured by [³H] proline incorporation. This activity was not associated with TSAb activity in 50% of the IgG preparations, and it was not found in IgGs from 7 of 8 patients with Graves' hyperthyroidism but no ophthalmopathy. Tao *et al.* [38] found that the serum of 20 patients with Graves' dermatopathy markedly stimulated the synthesis of DNA, protein and glycosaminoglycans by FRTL-5 cells, whereas assays of serum from 38 of 40 patients with Graves' disease without dermatopathy did not stimulate these processes more than normal serum. TSAb activity is measured by cAMP production by cultured functional rat thyroid lined (FRTL-5) cells. These reports suggest that only part of immunoglobulin components assayed as TBII or TSAb activity may stimulate retroorbital tissue. In fact, the presence of TSH receptor mRNA [39, 40] or its protein [41] in retroorbital tissue has recently been reported and hypothyroid patients with activities of thyroid stimulation-blocking antibodies are, for the most part, lacking in eye signs. TSAb may be involved in TAO, including the stimulation of glycosaminoglycans in retroorbital tissue. More specific methods are desired for autoantibodies to retroorbital tissue, including those mentioned above.

The sex distribution is more nearly equal in patients with overt ophthalmopathy than in those with Graves' hyperthyroidism [2]. The reasons are unclear, but the fact that the smoking habit is more prominent in men may be related. An association has been reported between TAO and smoking [42, 43]. There was a significant dose effect and worse grades of ophthalmopathy correlated with increased smoking. Our results were compatible with

these findings, and the mean initial EME value was significantly higher in smokers than in non-smokers and higher in male than in female patients, but the mean degree of improvement in EME was much higher in female than in male patients. On the other hand, it was not the case between smokers and non-smokers, namely, the present therapy was effective enough in both smokers and non-smokers. These results suggest that males and smokers in TAO belong to different populations.

In summary, the present study indicates that

high-dose intravenous steroid pulse followed by oral steroids is effective and safe for TAO.

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