

The long-term follow-up of patients with thionamide-treated Graves' hyperthyroidism

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Abstract. Since there have been few reports on the long-term prognosis of Graves' hyperthyroidism, the prognosis of 549 Graves' hyperthyroidism patients initially treated with thionamide and followed for >8 (range: 8.6–36.4) years was studied, evaluating the change in the TSH binding inhibitor immunoglobulin activity (TBII). The distribution of the time required for the first disappearance of TBII was normal after logarithmic conversion, and the mean \pm 2 SD was 1.5 (0.3–8.1) years. TBII became negative once within 5 years in 78.9% of patients. However, TBII re-elevation was observed in 47.8% of this group (fluctuating type). Remission was observed in 88.9% of the non-fluctuating type (smooth remission) and 37.2% of the fluctuating type patients. TBII remained positive for >5 years in 21.1% (smoldering type) of patients, with remission observed in only 19.8% of patients. Final remission was observed in 301 (54.8%) patients; the median time to remission was 6.8 (interquartile range: 4.0–10.9) years. A longer time until normalization of TBII and higher final thyroid weight were associated with a poor prognosis. Spontaneous hypothyroidism was observed in 6.0% of patients, independent of the TBII change. Our findings suggest that remission of Graves' hyperthyroidism mostly occurred after 4–11 years treatment. While predicting the prognosis before therapy was difficult, the clinical course may suggest a better prognosis if TBII disappears within five years without TBII fluctuation or enlargement of the goiter. Patients may safely wait more than five years to undergo ablative therapy if they hope to avoid permanent hypothyroidism.

Key words: Hyperthyroidism, Antithyroid drug, Graves' disease, Thyroid, TSH receptor antibody

MORE THAN HALF A CENTURY has passed since thionamide drugs [1] and radioactive iodine therapy (RAI) [2] were first used to treat Graves' hyperthyroidism (GD). Although well-established guidelines have been published [3, 4], the first-choice treatments for this disease varies among different countries. Despite a report recommending long-term antithyroid drug (ATD) therapy in 1979 [5], RAI remained the therapy of choice for 69% of expert thyroidologists in the USA in 1991 [6], probably because of the low remission rate reported after the introduction of iodide repletion [7]. In contrast, 77% of European thyroidologists and 88% of Japanese ones chose ATD as the first-line therapy [6]. While a shift away from RAI therapy toward ATD therapy was recently reported in the USA [8], a shift toward RAI therapy began in Japan when out-patient RAI therapy became available in 1998.

The overall remission rate after ATD therapy is

approximately 50%, (range, 45%–72%) [5, 9-22]. However, factors that can be used to discriminate patients in whom remission is likely from those who are likely to suffer a relapse remain unclear. Furthermore, it is difficult to evaluate the remission rate because considerable numbers of patients have been treated by ablative therapy.

TSH binding inhibitor immunoglobulin activity (TBII) or TSH receptor antibody (TRAb) was found to be associated with the pathogenesis of GD as a simple marker of the disease activity [17, 18, 23-29]. However, the value of TRAb measurement as a marker for remission still remains controversial.

There are two main ATD treatment protocols. The most popular one, according to the American and European Thyroid Association guidelines [3, 4], is to continue the drug for a particular interval (approximately 12–18 months) and then discontinue it once the TRAb levels have normalized, while continuing ATD therapy or switching to another definitive therapy with RAI or surgery if the TRAb level is persistently elevated [3, 4, 9-11, 14, 16, 18-20, 30, 31]. However, whether or not a 12- to 18 months interval is appropriate remains unclear [30, 31]. In addition, the approximate remission rate and the interval necessary for remission after 12- to 18

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months treatment have also been insufficiently investigated. Alternatively, drug administration may be continued until GD is no longer present, regardless of the time taken to achieve this end [5, 13, 17]: however, the issue with this approach is that it is difficult to tell when patients have achieved remission.

In Japan, hospitalization used to be mandatory for RAI therapy due to government rules. Given the limited capacity of the radioisotope ward in our hospital, the first-choice therapy was ATD, such as with methylmercaptoimidazole (MMI) or propylthiouracil (PTU), from 1981 until 2001 [32, 33].

Very few studies have evaluated the long-term prognosis of GD in a large number of patients mainly treated by ATD for more than eight years [13, 15, 20-22]. Most of these studies refer to children taking long-term ATD therapy probably avoiding ablative therapy. We therefore retrospectively evaluated the changes in the TBII values of 549 patients with GD mainly treated by ATD and assessed the long-term prognosis after 8–30 years.

Materials and Methods

The prognosis of 549 patients with untreated GD who visited our hospital between 1981 and 2001 and were followed for 8–36 years was retrospectively evaluated. The diagnosis of thyrotoxicosis was made based on elevated serum free T_4 (fT_4) and/or free T_3 (fT_3) levels in association with a suppressed serum TSH level. GD was diagnosed based on TBII positivity, thyroid-stimulating antibody (TSAb) positivity and/or a diffuse high thyroidal radioactive iodine uptake (RAIU). Patients with painless thyroiditis or functioning thyroid nodules were excluded. The patients were mainly treated with 10–15 mg ($n = 450$) or 20–40 mg ($n = 91$) of MMI. In the patients who required the early normalization of the thyroid function, such as those with atrial fibrillation, potassium iodide (KI; 10–100 mg) was administered with MMI. Eight patients were initially treated with propylthiouracil (PTU) (150 [$n = 3$] or 300 mg [$n = 5$]). When patients exhibited signs and symptoms suggestive of adverse effects, the drug was changed from MMI to PTU ($n = 24$) or KI ($n = 44$) [34], or from PTU to MMI ($n = 2$).

The patients were followed for at least one year without ablative therapy. The patients were classified into four groups according to the pattern of TBII disappearance: A0, TBII negative from the start of treatment; A2, positive TBII became negative within 2 years; A5, positive TBII became negative in 2–5 years; and group B, TBII remained positive for >5 years.

Following the disappearance of the thyroid stimulation indices, including positive TBII or TSAbs, an elevated serum thyroglobulin (Tg) level and an enlarged goiter

[17], the patients were asked whether they wished to stop or continue the therapy. We take care to avoid a relapse of hyperthyroidism whenever possible, especially in elderly patients with heart diseases [17]. If a patient remained euthyroid (normal serum levels of fT_4 and TSH) for >1 year after the cessation of the drug and TBII remained negative, they were considered to have entered remission (R). Otherwise, they were classified into the non-remission group (NR). Patients who became spontaneously hypothyroid were not included in the remission group, because they required thyroid hormone replacement therapy. Patients who were treated with ablative therapy were classified into the NR group.

The serum levels of fT_3 , fT_4 , TSH, Tg, TBII, TSAbs, autoantibodies to Tg and thyroid microsomal antigen, the estimated thyroid volume and the 5-h RAIU were measured as previously reported [17, 32-36]. When the serum fT_4 level was above the upper limit of the assay, the serum samples were measured using diluted sample after the equilibrium dialysis method (Nihon Mediphsics Co. Ltd. Tokyo, Japan). The serum TBII level was mostly determined using a first-generation radioreceptor assay kits (Baxter Health Care Co., Ltd., Tokyo, Japan) (normal range <15%) from 1981 by Otsuka Assay Laboratories, Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan. Starting in 2004 during long-term follow up, TBII was measured using a second-generation TBII assay with the human recombinant TSH receptor (normal <1 IU/L; DYNOTest TRAb human kit, Yamasa Corporation, Chiba, Japan), and the results were expressed as the percent inhibitory activity. The correlation coefficient between these two methods expressed as the percent inhibitory activity was 0.8566 according a Spearman's analysis ($n = 1,987$).

The goiter size was estimated by palpation and sketching using fine translucent paper performed by the same doctor (KO) and calculated using the planimetry method of Allen and Goodwin [17]. The thyroid weight was estimated to be 10 g if the thyroid was not palpable. After the introduction of ultrasonography, the goiter size estimated by palpation was shown to be almost the same as that calculated using the following formula: $0.7 \times$ the maximum width (cm) \times the maximum thickness (cm) \times the maximum length (cm) for each lobe ($r = 0.8825$, $n = 1,105$).

Statistical analyses

Statistical analyses were performed using the JMP 12 software program (SAS Institute, Inc., Cary, NC, USA). Continuous data are presented as the mean \pm SD or the median (interquartile range), as appropriate. An analysis of variance was performed to test the normality of the data (Shapiro-Wilk test). Comparisons were made using

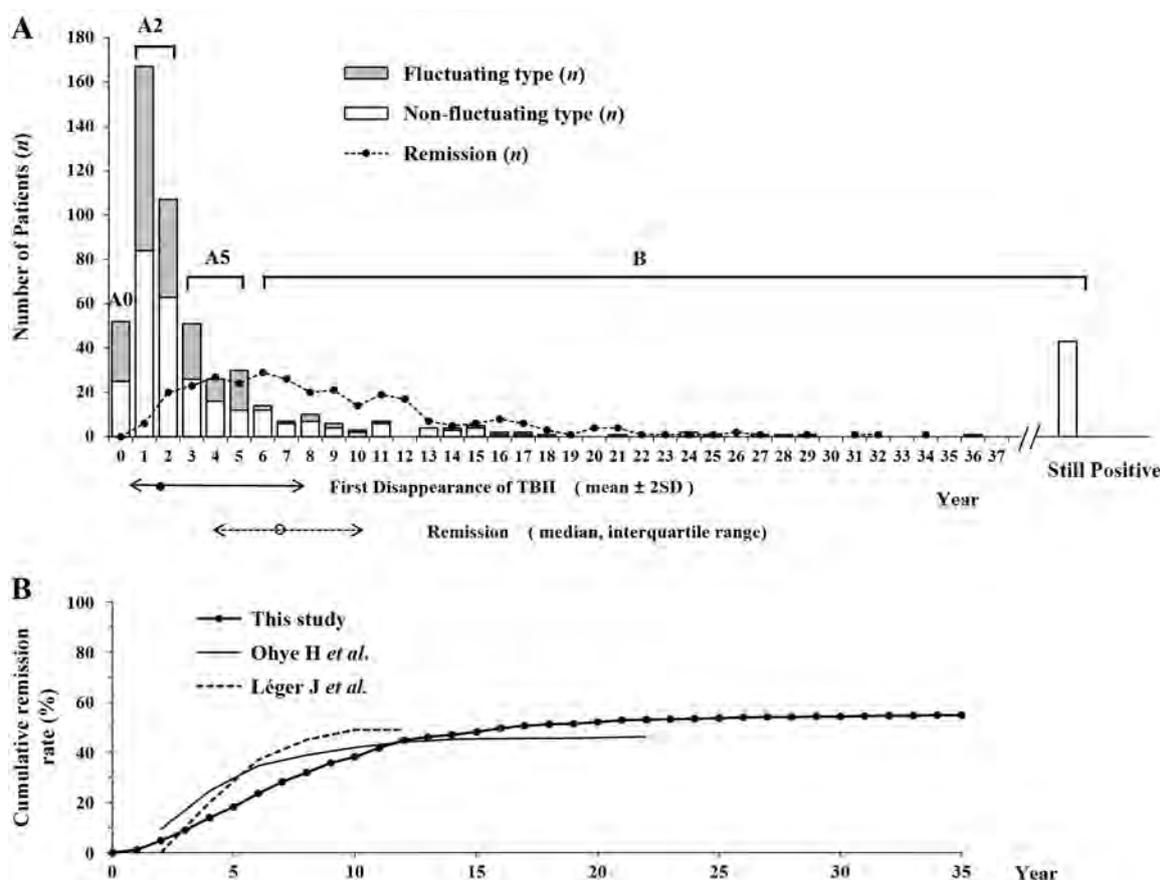


Fig. 1 A: Time until the first disappearance of serum TSH binding inhibitor immunoglobulin activity (TBII) after the initiation of thionamide treatment in the Graves' hyperthyroidism patients. The distribution pattern was normal after logarithmic conversion. The mean \pm 2 SD (1.5, 0.3–8.1 years, respectively) is shown. Patients who became TBII-positive again were classified as fluctuating-type (shaded). Forty-three (7.8%) of the patients remained TBII-positive during the observation period. Cases in which remission was achieved are indicated with closed circles.

B: The cumulative percentage of patients who entered remission is indicated with closed circles. The time until remission was 6.8 (4.0–10.9) years (median, interquartile range). Similar results reported in Graves' disease children by Léger J. *et al.* [20] and Ohye H. *et al.* [21] are shown for the comparison.

a multivariate logistic regression analysis. The lengths of time required for the goiter to shrink or the normalization of serum fT_4 , TSH and TBII level were compared using the log-rank test and Cox proportional-hazard model. *P* values of <0.05 were considered to indicate statistical significance.

The present study was approved by the Ethics Committee of Kyushu University.

Results

Time required for the first disappearance of TBII

As shown in Fig. 1A, the distribution of the time required for the first disappearance of TBII was shown to be normal after logarithmic conversion, and the mean \pm 2SD was calculated as 1.5 (0.3–8.1) years.

TBII was negative before treatment in 52 (9.5 %) of the patients, despite a high RAIU (group A0). Among

the other patients, TBII became negative within 2 years during continuous therapy in 274 (49.9%; group A2) and after 2–5 years continuous therapy in 107 (19.5%; group A5) patients. Thus, negative TBII was observed within 5 years in 433 (78.9%) patients.

TBII remained positive after more than 5 years of continuous therapy in 116 (21.1%) of the patients, suggesting a smoldering-type clinical course (group B). However, 73 of the smoldering-type patients later became TBII-negative, while 43 (7.8% of the total patients) remained TBII-positive throughout the observation period (Fig. 1A).

The number of patients who entered remission is also shown in Fig. 1A.

Re-elevation of the TBII activity: a fluctuating clinical course

In group A0 with negative TBII before treatment,

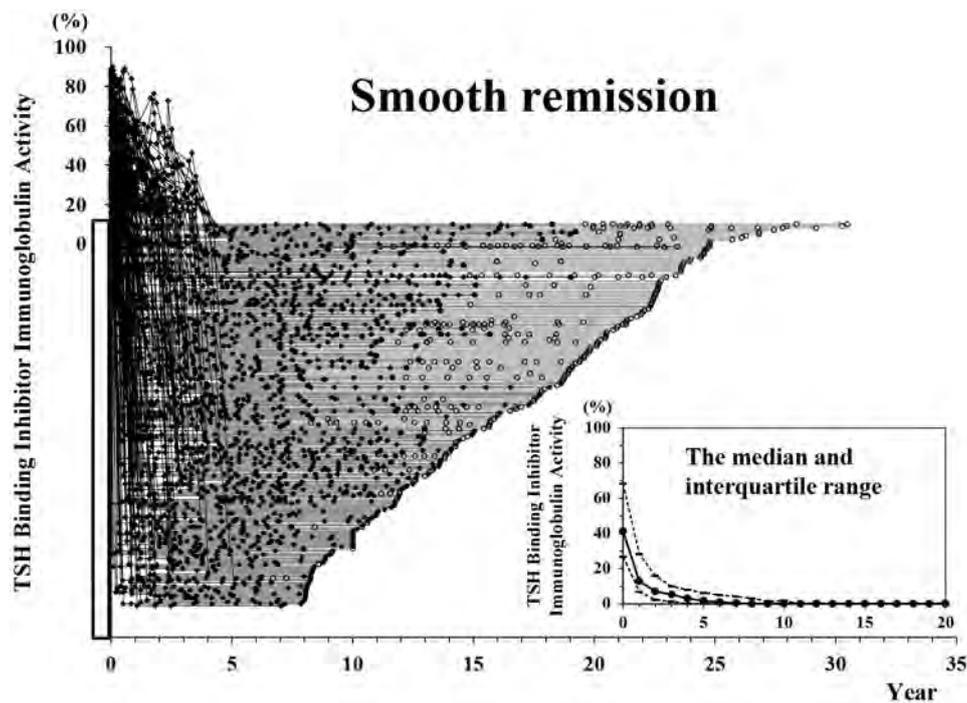


Fig. 2 The changes in the serum TSH binding inhibitor immunoglobulin activity (TBII) during the long-term follow-up of Graves' hyperthyroidism patients who were initially treated with thionamide. The patients in whom TBII became negative within five years and remained negative after remission (group A—smooth remission type). TBII values measured by the first-generation assay are shown by closed circle and values measured by the second-generation assay are shown by open circle and dotted line. The normal range of serum TBII levels is <15%, as shown by the white bar. In the framed area, the median and interquartile range of TBII are shown. Note the characteristics of the smooth remission group after the disappearance of TBII within 5 years without relapse observed in 36.6% of the total patients.

TBII became positive during treatment in 51.9% of the patients. After once disappearance of TBII within 5 years in groups A2 and A5, TBII remained negative in 53.6% and 50.5% but TBII re-elevation was observed in 46.4% and 49.5% of patients, respectively, as shown in Figs. 1A, 2 and 3. These patients with TBII elevation during clinical course were referred to as fluctuating-type cases. The prognoses of the groups A0, A2 and A5 were quite similar, including fluctuating-type in 51.9%, 46.4% and 49.5% of patients and final remission in 57.7%, 65.7% and 63.6% of patients, respectively. Therefore, groups A0, A2 and A5 were combined into group A (Table 1).

Among the 433 patients in group A, as shown in Table 1, TBII remained negative in 226 (52.2%), suggesting non-fluctuating type. In contrast, fluctuating type was observed in 207 (47.8%) while they were taking an ATD ($n = 176$) or long after the cessation of the drug ($n = 31$).

The long-term prognosis (smooth remission and remission after a fluctuating or smoldering course)

The long-term prognosis in each type is shown in Table 1. Remission was eventually observed in 201 (88.9%) of the 226 non-fluctuating patients in group A. These patients, accounting for 36.6% of the 549 total

patients, were considered to be in the smooth remission group, as shown in Fig. 2. In contrast, remission was observed in 77 (37.2%) of the 207 fluctuating-type patients in group A (Fig. 3).

In group B with smoldering TBII activity, 116 patients were continuously treated with ATD for more than 5 years (Table 1). The TBII activity gradually decreased after five years and remission was observed in 23 patients (19.8% of group B) (Fig. 4: upper). Among 86 patients in NR group in group B, 39 patients continued ATD (Fig. 4: lower) and 47 patients were treated with ablative therapy (Table 1). Between the smoldering group and smooth remission group, there was a considerable overlap in the initial TBII activity, but the difference was apparent after five years of treatment (Figs. 2, 4).

The high prevalence of fluctuating-type patients in group A prompted us to carefully continue a small maintenance dose of ATD for approximately 4.9 (2.0–7.7) (median, interquartile range) years, even after the disappearance of TBII in order to avoid relapse, taking into account other thyroid-stimulating factors, such as the goiter size, TSAbs, RAIU and serum Tg level [17]. After the withdrawal of ATD in 336 patients, early relapse occurred within 12 months in 4 (1.2%), late relapse

Table 1 The time required for the first disappearance of TSH-binding inhibitor immunoglobulin activity (TBII) and the long-term prognosis of the patients with Graves' hyperthyroidism who were initially treated with thionamide anti-thyroid drug

Group	A	B	Total
Time required for the first disappearance of TBII	<5 years	≥5 years	
Patients	433 (78.9%)	116 (21.1%)	549
Type	non-fluctuating	fluctuating ^a	smoldering
Re-elevation of TBII	(-)	(+)	
Patients (n)	226 (52.2% of A)	207 (47.8% of A)	116
(%/Total)	(41.2%)	(37.7%)	(21.1%)
	%/n	%/n	%/n
Remission	201 ^b (88.9%)	77 (37.2%) ^c	23 (19.8%) ^c
Spontaneous hypothyroid	14 (6.2%)	12 (5.8%) ^d	7 (6.0%) ^d
Non-remission (NR)	11 (4.9%)	118 (57.0%)	86 (74.1%)
Ablation therapy (% in each group)	5 (2.2%)	58 (28.0%)	47 (40.5%)
Ablation therapy (% in NR)	45.5%	49.2%	54.7%
Years required for remission ^e	5.9 (3.4–8.9)	9.5 (4.7–13.8)	12.1 (8.7–20.1)

^a Re-elevation of TBII was observed after once TBII became negative within 5 years.

^b Smooth remission group without fluctuating or smoldering TBII activity (36.6% of the 549 total patients)

^c Significantly different from the non-fluctuating A group ($p < 0.0001$).

^d No significant difference compared with the non-fluctuating A group

^e The values are shown as the median (interquartile range)

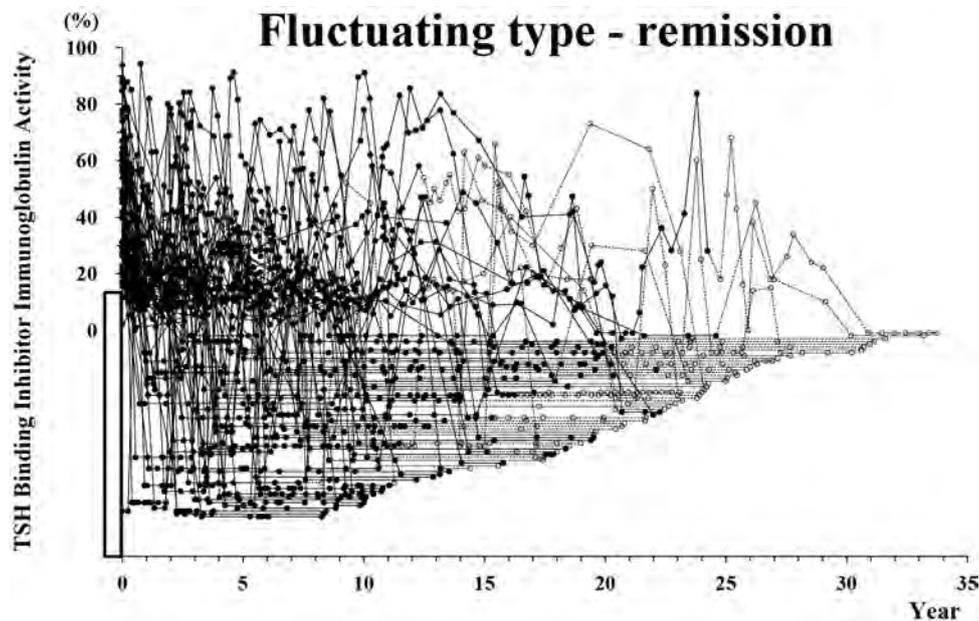


Fig. 3 The changes in the serum TBII in the fluctuating type group A patients. TBII was negative before therapy or positive TBII became once negative within five years, but an increase in the TBII activity was observed during the clinical course. Only the patients who went into remission without ablation therapy are shown. See legends for Fig. 2.

occurred at 12 months or later (13–228 months, median 48 months) in 31 (9.2%) and 301 patients (89.6%) remained in remission.

The time until remission was not normally distributed

at 6.8 (4.0–10.9) years (median, interquartile range) (Table 1, Fig. 1A). These patients remained euthyroid without ATD for 9.8 (4.2–15.2) years (Figs. 2–4). About 4% of the 549 patients went into remission every year

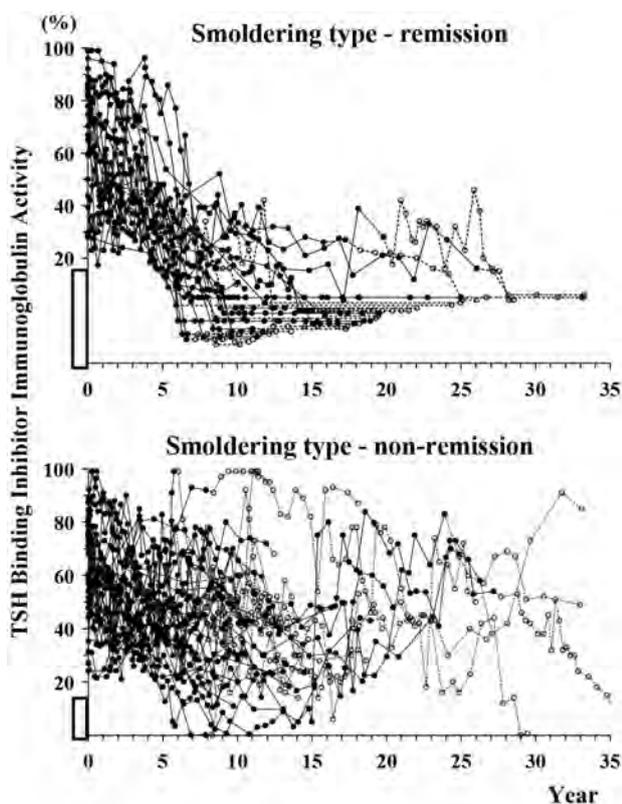


Fig. 4 The changes in the serum TBII in the smoldering type group B patients in whom TBII remained positive for more than five years. Upper: Remission group, Lower: Non-remission group. The data of the patients who were treated by ablation therapy are not shown. See legends for Fig. 2.

after 2–12 years (Fig. 1A). The cumulative percentage of patients who went into remission was 18.2% after 5 years, 38.3% after 10 years, 48.1% after 15 years, 52.1% after 20 years and 54.8% after 35 years (Fig. 1B). Fifteen (2.7%) patients were confirmed to have gone into remission after 20 years of treatment.

The long-term prognosis (spontaneous hypothyroidism)

As shown in Table 1, about 6% of the patients in each group became spontaneously hypothyroid during the clinical course without ablative therapy. The change in TBII activity was quite variable; remaining positive in 7 (21.2%) and becoming negative in 26 (78.8%) of patients.

The long-term prognosis (NR)

Excluding the patients with spontaneous hypothyroidism, remission was not achieved in 11 (4.9%) of non-fluctuating type group A, 118 (57.0%) of fluctuating-type group A and 86 (74.1%) of smoldering group B (Table 1). Some patients preferred to continue ATD ther-

apy, even after the disappearance of TBII. About half of the NR patients in each group were treated by ablative therapy (Table 1).

The clinical data of the R, NR and spontaneously hypothyroid groups

Regarding the factors predicting the prognosis, a multivariate logistic regression analysis of the clinical parameters before or during treatment was performed separately (Table 2). Even before treatment, the difference was significant ($p = 0.0192$) and NR was more frequently observed in male and younger patients, with the serum fT_3 level significantly lower in the spontaneously hypothyroid group than in the other groups (Table 2A). However, there was no significant difference in the severity of the disease before treatment, such as in the estimated thyroid volume, RAIU or serum fT_4 , fT_3 , TBII or TSAb levels. There were also no significant differences in the prevalence of complications, such as severe exophthalmos ($p = 0.4543$) and atrial fibrillation ($p = 0.1515$), or the presence of thyroid bruit ($p = 0.1117$), antithyroglobulin antibody ($p = 0.7778$) or anti-thyroid microsomal antibody ($p = 0.4963$).

In contrast, the difference was more prominent during treatment ($p < 0.0001$) (Table 2B). A longer time until the disappearance of TBII and palpable goiter, and a larger final estimated thyroid volume after drug treatment were significantly associated with a poor prognosis. There were no significant differences in the thionamide drugs used (MMI or PTU) ($p = 0.3177$), the initial dosage ($p = 0.1427$) or the presence of side effects ($p = 0.7713$), which was observed in 11.3%–14.9% of patients. The difference in the clinical course of the remission group and non-remission group was further evaluated by the log-rank test and Cox proportional-hazard model. The time required for the disappearance of palpable struma ($p < 0.0001$, hazard ratio (HR): 1.3514, 95% confidence interval (CI): 1.09–1.68) or normalization of serum TSH level ($p < 0.0019$, HR: 1.3663, CI: 1.14–1.64) was significantly longer in non-remission group

Comparison of the clinical data of the different group or different type GD

Clinical data including age, sex, serum fT_3 , fT_4 , TBII, TSAb, autoantibodies to Tg and thyroid microsomal antigen, estimated thyroid volume and 5-h RAIU before treatment were further compared using a multivariate logistic regression analysis between group A ($n = 433$) and group B ($n = 116$) or between smooth remission type ($n = 201$, Fig. 2) or fluctuating type ($n = 207$) group A patients.

Between group A and group B, the difference was sig-

Table 2 The prognosis of the 549 patients with Graves' hyperthyroidism who were initially treated with thionamide drugs

	Remission	Non-remission	Spontaneous hypothyroid	<i>p</i> value ^f
<i>n</i> (%)	301 (54.8%)	215 (39.2%)	33 (6.0%)	
(A) A comparison of the clinical data before the treatment				0.0192
Sex (Male:Female)	55:246 (Male 18.3%)	52:163 (Male 24.2%)	4:29 (Male 12.1%)	0.0132
Age (years)	38.4 ± 14.4	35.9 ± 13.3	40.7 ± 14.1	0.0075
Estimated Thyroid Volume (mL)	31 (23–45)	30 (21–43)	29 (23–44)	0.4074
RAIU ^a (%/5h)	60.0 (39.5–71.6) [278]	53.1 (36.6–69.5) [197]	58.7 (45.0–75.3) [31]	0.2488
freeT ₄ (ng/dL)	6.3 (4.0–9.6)	6.1 (4.2–9.0)	6.4 (3.3–8.0)	0.0974
freeT ₃ (pg/mL)	16.4 (10.6–22.7) [215]	16.0 (11.2–21.0) [158]	15.2 (8.4–20.9) [22]	0.0276
Serum TBII ^b (%)	42.4 (27.6–66.4)	49.5 (27.5–73.3)	46.7 (30.8–76.5)	0.0630
Serum TSAAb ^c (%)	255 (146–483) [263]	277 (137–827) [194]	338 (215–1,198) [27]	0.0524
(B) A comparison of the clinical data during the treatment				<0.0001
– Abnormal data observed ^d				
Serum free T ₄ (days)	45 (28–85)	54 (30–101)	41 (19–76)	0.2771
Serum TSH (days)	237 (98–536) [296]	309 (108–929) [211]	276 (85–580)	0.2659
Serum TBII ^b (days)	392 (160–882)	1,004 (286–3,781)	500 (287–1,647)	0.0002
Struma (palpable) (days)	1,132 (284–2,701) [254]	1,831 (317–3,653) [152]	2,604 (1,114–4,334) [29]	0.0064
Final estimated thyroid volume (mL) ^e	10 (10–18)	30 (18–50)	10 (10–23)	<0.0001
Withdrawal of antithyroid drug (years)	6.8 (4.0–10.9)		7.0 (2.1–10.3)	
Follow-up period (years)	18.4 (11.9–22.8)	18.5 (12.6–23.7)	22.7 (16.3–25.9)	0.0741
Ablation time (years)		7.5 (4.4–11.5) [112]		

The number in square brackets is the number of the patients measured. Otherwise, all patients were measured.

The values are shown as the mean ± SD or median (interquartile range).

^a RAIU, radioactive iodine uptake, ^b TBII, TSH binding inhibitor immunoglobulin activity, ^c TSAAb, thyroid-stimulating antibody

^d The days required for the first normalization of each parameter. If the parameter did not normalize during the observation period, the last visit date was used for the calculation.

^e Estimated thyroid volume at the last visit, or at the time of ablation in the ablated patients. ^f Comparison between three groups.

nificant ($p < 0.0001$) because of the high TBII value (median value 38.4 vs. 68.4% $p < 0.0001$) found in group B. There were no other significantly different factors. Between smooth remission type and fluctuating type group A, there were no significant differences ($p = 0.1007$) in the clinical data before treatment.

As to the difference in the clinical course between group A and group B, it took significantly longer time before the normalization of serum fT₄ (median value, 45 vs. 63 days, $p < 0.0001$, HR: 1.5236, CI: 1.24–1.89) and serum TSH level (217 vs. 581 days, $p < 0.0001$, HR: 1.9492, CI: 1.58–2.43) or the disappearance of struma (1,140 vs. 2,695 days, $p < 0.0012$, HR: 1.5260, CI: 1.18–1.99) in group B. Between smooth remission type and fluctuating type group A, there were no significant differences in the improvement of serum fT₄ level (42 vs. 49 days, $p = 0.2777$, HR: 1.1127, CI: 0.92–1.35) and first disappearance of serum TBII (355 vs. 336 days, $p = 0.3173$, HR: 1.1047, CI: 0.91–1.35) but it took slightly

longer time before the normalization of serum TSH level (205 vs. 220 days, $p = 0.0207$, HR: 1.2666, CI: 1.04–1.55) or the disappearance of struma (1,036 vs. 1,442 days, $p < 0.0001$, HR: 1.6244, CI: 1.29–2.04) in fluctuating type group A.

Discussion

We evaluated the change in TBII and the long-term prognosis of 549 patients with GD. There were six important findings. First, the distribution of the time until the first disappearance of TBII was normal after logarithmic conversion (Fig. 1A). The disappearance of TBII was first observed 1.5 (0.3–8.1) years after the initiation of ATD treatment, partially justifying the recommendation to continue ATD for approximately 12–18 months by guidelines [3, 4]. About two years on average might be required for the active B cells to stop producing TBII during ATD treatment. However, it also suggested that

TBII remained positive for longer periods in another half of the patients. Second, moreover, re-elevation of TBII was observed in approximately half of these patients who became TBII-negative within five years suggesting fluctuating clinical course. Third, the absence of TBII before treatment (A0) or the disappearance of TBII within two years (A2) did not suggest a better prognosis than in patients in whom TBII disappeared between two and five years (A5) after the initiation of the treatment, despite reports suggesting a better prognosis when the early disappearance of TBII was observed [26, 27]. However, the prognosis of these patients in group A was far better than that of the patients in group B in whom TBII remained positive for more than 5 years. Fourth, smooth remission was achieved in about one-third of GD patients in whom ablative therapy might not be necessary. Fifth, even in fluctuating-type group A and smoldering type group B, final remission was observed in 37.2% and 19.8% of the patients, respectively, after a long clinical course of more than 8 years. Sixth, spontaneous hypothyroidism was observed in about 6% of patients, irrespective of the changes in TBII activity. These points suggest the presence of immunological heterogeneity among the patients with GD.

The high prevalence of fluctuating-type patients clearly confirmed the limited role of TBII in predicting remission. Although TBII positivity strongly suggests that GD remains immunologically active and requires continued ATD therapy [17, 18, 24, 25], the disappearance of TBII does not necessarily suggest the remission of the disease. In group A, re-elevation of TBII was observed in about a half of patients, and 129 (29.8%) of the patients were ultimately classified into the NR group despite the disappearance of TBII within 5 years (Table 1). This value was strikingly close to that reported by Feldt-Rasmussen *et al.* [25], who reported that the relapse rate of GD in TBII-negative cases was 25%. Thus, TBII is not a satisfactory marker for predicting remission, even when it is measured by a highly sensitive method [28].

Fluctuation of TBII activity usually occurred while the patients were still taking ATD. That was the reason for us to use thyroid stimulating indices such as TSAb, estimated thyroid volume, serum Tg level and sometimes RAIU, in addition to TBII, before the decision to withdraw ATD [17]. After the withdrawal of ATD in our previous study, early relapse occurred within 12 months in all the patients when more than three thyroid stimulation indices were positive, early relapse occurred in 65–71% and late relapse occurred at 12 months or later in 2–11% of the patients when one or two indices were positive, while 86% of the patients remained in remission when all the indices were negative [17]. After the withdrawal

of ATD in this study, remission was observed in 89.6%, early relapse occurred in 1.2% and late relapse occurred in 9.2%, suggesting the difficulty in predicting late relapse of GD. However, remission was finally observed in 201 (88.9%) of the 226 patients in non-fluctuating type group A (Fig. 2) and in 77 (37.2%) of the 207 patients in fluctuating-type group A (Table 1, Fig. 3).

The possibility of remission in smoldering group B was lower than that in group A (Table 1, Fig. 4). However, approximately 20% of these patients eventually went into remission after 5–30 years of tenacious treatment (Figs. 1, 4). Our study suggested that remission could be expected, even in fluctuating-type or smoldering-type patients, if they were followed for >5 years with ATD. This is in line with the findings of Lippe *et al.*, who reported a 25% remission rate every 2 years, regardless of the duration of previous therapy, in hyperthyroid children who received long-term medical therapy [13].

In our study, 301 (54.8%) of the 549 patients with GD experienced remission after ATD treatment (Table 1, Fig. 1). Although the median time to remission was 6.8 (4.0–10.9) years, 201 (36.6%) of the patients achieved smooth remission after the disappearance of TBII within 5 years, and TBII remained negative for 15.7 (4.3–30.8) years (Fig. 2), suggesting only 1 episode of GD during their lifetime, similar to the clinical course of measles. The cumulative remission rate in children is reported to be approximately 25%–30% after 5 years and 40%–45% after 10 years [20, 21] (Fig. 1B). Our study suggested a similar remission rate even in adult patients, although it took a few years longer before remission was achieved, because we cautiously avoided stopping ATD in order to prevent relapse. The duration of ATD treatment may be an important factor that is associated with the likelihood of remission.

Of note: 57.0% of the fluctuating-type group A patients and 74.1% of the smoldering-type group B patients were classified into the NR group. However, it must be pointed out that approximately half of the NR patients underwent ablative therapy 7.5 (4.4–11.5) years after the initiation of the treatment.

With regard to the outcomes of ATD therapy, Wartofsky *et al.* reported markedly reduced remission rates, with remission observed in only 6 (13.6%) of 44 patients, in 1973 [7]; this appeared to be related to an increased dietary intake of iodine. The results reported in that paper might have led to changes in the criteria for patient selection for the various forms of hyperthyroidism therapy after the introduction of iodide supply. It might therefore be appropriate to consider ablative therapy early, rather than continuing long-term ATD therapy, in areas with a high iodine intake. However, it must be noted that the

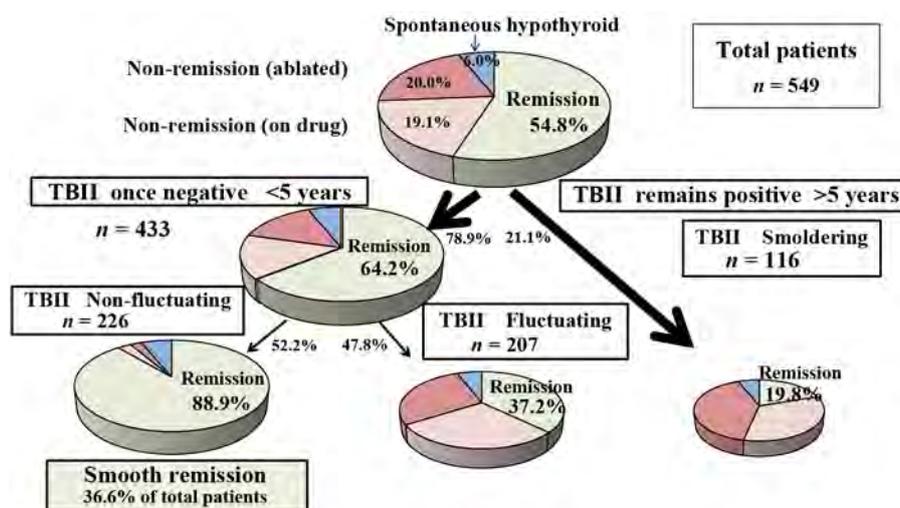


Fig. 5 The expected remission rate in the patients with Graves' hyperthyroidism depending on the change in serum TSH binding inhibitor immunoglobulin activity (TBII), based on the long-term follow-up of the patients initially treated with thionamide drugs. These data may help patients choose or change their therapy during antithyroid drug treatment.

follow-up period in that study was short (7–46 months: average, 17.6 months), and 31 of the patients received RAI or thyroidectomy within 3 years. The same group later reported that sustained remission was achieved in 35 (50.7%) of the 69 patients, probably because their average dietary iodine content had been decreasing [12]. Our study in Japan, a country that is well known to have a sufficient intake of iodine, suggested that the remission rate was 54.8%, which is almost the same as that reported in other countries [5, 9–22]. It seems best to treat a controllable, self-limited disease with a controllable and limitable therapy in order to avoid inducing permanent hypothyroidism, which requires life-long replacement therapy [5]. It must be kept in mind that early ablative therapy reduces the remission rate.

It was interesting to find that approximately 4%–6% of the patients became spontaneously hypothyroid [37] in almost every group, despite the difference in TBII activity (Table 1). The prevalence of hypothyroidism was almost the same as that in the general population of this area [38], suggesting that concomitant chronic thyroiditis [37] with histological changes in the thyroid gland itself [36, 39] might be responsible for hypothyroidism, irrespective of the change in TBII activity.

Our data were summarized in Fig. 5. Ablative therapy should be considered for fluctuating-type patients, even if TBII disappears within 5 years, who do not wish to frequently visit a hospital when a relapse occurs. Ablative therapy should also be considered in smoldering-type patients who wish to avoid more than five years of ATD therapy. Even in smoldering-type, remission can be expected after 8–30 years treatment (Fig. 1), but the remission rate is estimated to be 20%. If patients are able

to continue taking the drug with good compliance and without adverse effects, ATD therapy can be carefully continued before definitive treatment is envisaged. The tenacious continuation of daily low-dose ATD therapy has been shown to be safe [5, 40] and can be selected for patients who wish to avoid permanent hypothyroidism. Remission or spontaneous hypothyroidism could be expected in about two-thirds of the total patients, but it may take 4–11 years (median 7 years) (Fig. 1). As an auto-immune abnormality, 50% remission after 10 years' treatment found in GD is far better than only 7.1% prolonged complete remission reported in systemic lupus erythematosus [41]. The immunological abnormalities responsible for the fluctuation in TBII activity should be clarified in the future.

Recent studies [42–44] and systematic reviews and meta-analyses [45] have suggested several pretreatment risk factors of relapse, but the small predictive power of a single risk factor is insufficient to predict the outcome of a single patient. In our study, it was also difficult to predict the initial response to ATD or the long-term prognosis from the initial parameters. However, it became easier to predict the prognosis during treatment (Table 2B). The persistence or further enlargement of an enlarged thyroid gland and the persistence of positive TBII were the most significant poor prognostic factors. Treatments must be selected by the patient and for the patient while considering the expected remission rate, depending on the clinical course (Fig. 5). The use of ATDs for longer periods of at least three to six years may be required to achieve a better rate of remission [46] not only in children but also in adults.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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