Endocrine Journal 2007, **54** (5), 713–720

Prognostic Value of Thyrotropin Receptor Antibodies (TRAb) in Graves' Disease: A 120 Months Prospective Study

CARLO CAPPELLI, ELENA GANDOSSI, MAURIZIO CASTELLANO, CLAUDIO PIZZOCARO*, BARBARA AGOSTI, ANDREA DELBARBA, ILENIA PIROLA, ELVIRA DE MARTINO AND ENRICO AGABITI ROSEI

Department of Medical and Surgical Sciences, Internal Medicine and Endocrinology Unit, University of Brescia, Brescia, Italy
**Department of Radiology, Spedali Civili of Brescia, Brescia, Italy*

Abstract. In most trials, at least 30–60% of patients with Graves' disease treated with antithyroid drugs relapse within 2 years after therapy withdrawal. At present, there are no prognostic parameters available early in treatment to indicate patients likely to achieve long-term remission. Because thyrotropin receptor autoantibodies (TRAb) are specific for Graves' disease, we evaluated the ability of their levels and of their rate of change to predict long-term prognosis. In our study 216 consecutive patients with newly diagnosed Graves' disease started a therapy with methimazole. Patients were treated until they achieved euthyroidism and TRAb were measured at 6-month intervals throughout a follow up of 120 months. Our study demonstrated that at the onset of hyperthyroidism patients' age, sex, fT4 levels and goiter size had no prognostic value in predicting long-term prognosis (respectively $p = 0.79$; $p = 0.98$; $p = 0.83$; $p = 0.89$). On the contrary, at the time of diagnosis TRAb titer was a good predictor of the final outcome ($p<0.001$); a titer equal to (or) more than 46.5 UI/L could identify patients who had never achieved long-term remission with a sensitivity of 52% and a specificity of 78%. Also fall rate of TRAb at 6 months of follow up and after therapy withdrawal were useful to predict the final outcome ($p<0.001$). At 6 months of follow up the time of therapy withdrawal, a decrease of TRAb lower than 52.3% or even its increase could identify patients who had never achieved permanent remission with a sensitivity of 55% and a specificity of 79.1%. No single parameter among TRAb, satisfactory identified a sub-set of patients who achieved long remission. Accordingly to our data, the best result in predicting long term remission is probably given by the presence of at least one of the two features evaluated at 6 months (TRAb titer and/or percentage of TRAb fall rate), with a sensitivity of 63% and specificity of 88%. TRAb titers evaluated both at the onset of hyperthyroidism that at 6 months of therapy or their rate of fall at 6 months and at ATD withdrawal are predictors of outcome. However, the presence of at least one, between titers of TRAb or their rate of fall at six months, resulted to be the best predictor of remission with the higher sensitivity and specificity.

Key words: Thyroid antibodies, Graves' disease, Hyperthyroidism, Prognosis

(*Endocrine Journal* **54**: 713–720, 2007)

GRAVES' disease (GD) is an autoimmune disorder, characterized by the presence of circulating thyrotropin receptor auto antibodies (TRAb) [1]; the thyroid-stimulating activity of TRAb is responsible for the development of hyperthyroidism. Treatment strategies for Graves' hyperthyroidism include medical therapy with antithyroid drugs (ATD), or thyroid ablation with radioiodine or surgery [2]. Conservative therapy with ATD is the first choice treatment in Europe [3] and drug selection is largely determined by local practice, methimazole being mostly used. A long-term treatment of about 12–18 months is usually adopted, which requires careful monitoring of patients for side effects such as allergic reactions, agranulocytosis and hepatotoxicity [4, 5]. At therapy withdrawal, relapse rate is very high (50–60%), and many patients need further treatment [6, 7]. Therefore, some authors, particularly

Received: April 12, 2006
Accepted July 23, 2007
Corresponding to: Dr. C. CAPPELLI, Department of Medical and Surgical Sciences, Internal Medicine and Endocrinology Unit, University of Brescia, c/o 2^ Medicina Spedali Civili di Brescia, Piazzale Spedali Civili n°1, 25100 Brescia, Italy

in the United States, favor thyroid ablation as the first choice treatment in most instances [7]. On the other hand, ablative treatment is not devoid of unwanted side-effects. Thyroid surgery entails perioperative morbidity, postoperative hypothyroidism, and hospitalization costs [2]; radioiodine treatment, in turn, implies subsequent hypothyroidism and the possibility of secondary neoplasia [8].

Therefore, one major issue with GD is the identification of patients likely to achieve long-term remission after conservative therapy [7, 9–11]. Assessing prognostic parameters may be useful to select those patients who are unlikely to benefit from ATD and consequently directly suitable for an ablative treatment which would spare a long, useless and potentially harmful pharmacological therapy.

The role of TRAb levels, as a predictor of outcome for ATD treatment, is rather controversial [10–14]: many variables, such as prospective vs retrospective studies, laboratory methods adopted to evaluate TRAb (TBII vs TSab), time of TRAb measurement (basal vs post-therapy values) and ATD treatment (type, dosage and duration) give complicated the overall interpretation of this issue.

Ideally, TRAb levels would be a very useful clinical tool if their measurement, at the time of diagnosis and/or TRAb level changes during ATD treatment, could discriminate with sufficient specificity and sensitivity, those patients who benefit from a short-term ATD course from those who require a more prolonged ATD treatment or must be assigned to ablative treatment options.

To further explore this hypothesis, we designed a prospective study aimed to investigate, the role of TRAb titer, as well as other potential predictors, in achieving long term remission after ATD treatment.

Materials and Methods

Patients

From January 1993 to January 1995, we evaluated 216 consecutive patients (31 males and 185 females) with newly diagnosis of GD, at the outpatient clinics of the Endocrinology Unit of the University of Brescia and the Nuclear Medicine Unit of Spedali Civili of Brescia. The diagnosis of GD was based on commonly accepted clinical and laboratory criteria: hyperthyroidism, diffuse goitre without nodular formations at ultrasound, uniform pattern of uptake on scan with Tc-99m, presence in serum of TRAb. Hyperthyroidism was diagnosed on the basis of signs and symptoms of thyrotoxicosis, even without infiltrative opthalmopathy, and on the basis of raised free thyroxin (fT4) levels with undetectable thyrotropin (TSH). Thyroid volume was assessed at diagnosis by ultrasound in all patients, using the ellipsoid formula (normal values <18 mL in males, <14 mL in females).

Study protocol

According to the study protocol, all patients started therapy with a standard dose of methimazole (20 mg/day). A follow-up was planned up to 120 months, with control visit every three months during the first year, and every six months later on. A careful medical examination and laboratory assessment of TRAb, TSH and fT4 level were performed at any visit. The same examination was performed at therapy withdrawal. Accordingly, pharmacological therapy was adjusted to keep euthyroid status, when TSH was at or above normal range levels and fT4 at or below serum level. When a condition of "euthyroidism" was achieved, patients were immediately treated with 2.5 mg of methimazole for 3 further months. After therapy withdrawal, if a relapse occurred (clinical and biochemical signs of hyperthyroidism), treatment with methimazole at the same dosage (20 mg/day) was restarted.

Patients were eligible for ablative treatment (surgery or radioactive iodine) if they a) showed adverse drug reactions; b) relapsed at least three times after therapy withdrawal; c) had relevant symptoms related to tracheal compression; or d) did not achieve a condition of euthyroidism after at least one year of consecutive methimazole treatment (20 mg/day).

All the patients enrolled in this study completed the 120 month follow-up period, unless they were submitted to ablative treatment. At the end of the observation period, patients were assigned to four categories, as follows: Group 1 included those patients who achieved long-term euthyroidism (at least 48 months) after therapy withdrawal and had no relapse; Group 2 included patients who achieved long-term euthyroidism after at least one relapse; Group 3 consisted of patients submitted to ablative treatment (surgery or radioactive iodine) after at least three transitory remissions and subsequent relapses; Group 4 included patients who underwent

ablative treatment without any prior evidence of remission. Groups 1 and 2 were collectively included in the "Remission" category (REM), whereas groups 3 and 4 were considered as an "Ablation" (ABL) category.

The study was conducted according to the principles of the Helsinki declaration and the guidelines of the institutional ethical committee. Written informed consent was obtained from all subjects.

Methods

Serum free thyroxin (fT4) was determined by commercially available radioimmunoassay (fT4 RIA CT-RADIM, Rome, Italy; range: 8.0–18.0 pg/ml); serum thyroid stimulating hormone (TSH) was measured by a sensitive immunoradiometric assay (TSH IRMA Co Tube 2nd generation; range: 0.2–4.0 mIUI/L-BIORAD, Hercules, CA, USA).

TSH receptor antibodies (TRAb) were determined by a commercial RRA (TRAK-Assay, B.R.A.H.M.S: Diagnostica; normal range <9 UI/L).

Statistics

Differences among subgroups of patients, at baseline or at different time-point during follow-up, were evaluated by ANOVA. Linear association between the parameters under examination was evaluated by Pearson correlation analysis. To evaluate the influence of fT4 and TRAb titer on prognosis, *i.e.* remission vs. thyroid ablation, logistic regression analysis was used (with age, thyroid size and sex as covariates). The sensitivity and the specificity of TRAb and fT4 cut-off were determined by the ROC-curve method [15]. Event-free survival (relapse/thyroid ablation after ATD treatment) was documented using a Kaplan-Meier curve. A p value ≤0.05 was considered statistically significant. Values are presented as mean ± standard deviation. Data were analyzed with SPSS for Windows (realized 12.0).

Results

Of the 216 patients who completed the follow-up, 71 (32.9%) achieved long-term euthyroidism after ATD withdrawal without relapse (Group 1); 20 (9.2%) patients achieved long-term euthyroidism after at least one relapse (Group 2); 76 (35.2%) subjects underwent ablative treatment (surgery or radioactive iodine) after many transitory remissions and subsequent relapses (Group 3); 49 (22.7%) patients never achieved remission on ATD treatment and underwent ablative treatment (Group 4). Accordingly, at the end of follow up, 91 patients (Group 1 and 2) achieved long-term remission (REM) and 125 patients (Group 3 and 4) underwent ablative treatment (ABL). Among ABL groups two subjects were submitted to ablative treatment because showing symptoms of tracheal compression after a mean period of 9 months of ATD. All the others patients were submitted to ablative treatment because they didn't achieve euthyroidism after at least one years of therapy and/or relapsed at least three times after therapy withdrawal. No drug side effects were observed in our study; consequently no patients were submitted to ablative treatment for this reason.

Table 1 summarizes the clinical characteristics of patients at entrance in the study, as a whole and in separate groups, according to the above definitions.

Table 1. Clinical characteristics of patients at the time of diagnosis

	Group 1	Group 2	Group 3	Group 4	REM (Group 1, 2)	ABL (Group 3, 4)	All Patients
N°	71	20	76	49	91	125	216
Age (years)	39.9 ± 11.2	36.0 ± 11.4	37.6 ± 13.4	42.6 ± 14.9	37.9 ± 11.3	40.1 ± 13.9	39.4 ± 13.1
Sex: F (%)	85.9	85.0	84.2	87.8	85.7	85.6	85.6
fT4 (pg/ml)	42.6 ± 16.4	52.9 ± 18.6**	43.4 ± 20.3	48.5 ± 19.4	44.8 ± 17.4	45.4 ± 20.1	45.2 ± 18.9
TRAb (UI/L)	39.7 ± 40.3	51.7 ± 77.8§	63.4 ± 84.5§	124.1 ± 115.9§	42.4 ± 50.6	87.2 ± 102.1*	68.4 ± 87.0
Size (<40 mL)	35%	35%	30%	34%	35%	32%	33.3%
Size (40–70 mL)	51%	50%	54%	53%	51%	54%	52.3%
Size (>70 mL)	14%	15%	16%	13%	14%	14%	14.4%

*p<0.001 REM vs ABL, **p<0.001 Group 1 vs Group 2, §p<0.001 Group 1 vs Group 2, Group 3 and Group 4

Table 2. Details of duration of therapy, time lapsed from diagnosis to first therapy withdrawal; time lapsed from therapy withdrawal to first relapse and percentage of TRAb fall rate at the therapy withdrawal and at 6 months of follow-up

	REM		ABL	
	Group 1	Group 2	Group 3	Group 4
Time lapsed from diagnosis to first therapy withdrawal (months)	13.9 ± 7.1	7.8 ± 5.5*	8.2 ± 7.0*	—
Time lapsed from therapy withdrawal to first relapse (months)	—	14.4 ± 9.3	7.5 ± 6.4**	—
Number of relapses (average, range)	—	1.05 (1–2)	1.48 (1–3)	—
Total duration of ATD therapy (months)	13.9 ± 7.1	19.6 ± 6.6°	21.2 ± 4.3°	28.2 ± 15.4§
TRAb rate of fall at 6 months of follow up (%)	42.8	48.1	29.9°°	–11.1^
TRAb rate of fall at therapy withdrawal (%)	68.3	54.3^^	38.7^^	—

*p<0.001 Group 1 vs Group 2 and vs Group 3, **p<0.05 Group 2 vs Group 3, °p<0.05 Group 1 vs Group 2 and vs Group 3, §p<0.001 Group 1 vs Group 4, °°p<0.01 Group 1 and Group 2 vs Group 3, ^p<0.001 Group 1 and Group 2 and Group 3 vs Group 4, ^^p<0.001 Group 1 vs Group 2 and Group 3

Table 3. Multivariate predictors of risk of first relapse after therapy withdrawal

Predictors	OR (95% CI)	Wald statistics
Age	0.9 (0.7–1.3)	NS
Gender (male)	0.8 (0.6–1.7)	NS
Thyroid size	1.0 (0.8–1.2)	NS
fT4	1.2 (0.9–1.5)	P<0.001
TRAb levels	0.9 (0.6–1.1)	NS

Abbreviations: OR, odds ratio; CI, confidence interval; NS, not significant

Table 4. Multivariate predictors of following ablative treatment

Predictors	OR (95% CI)	P Value
Age	1.0 (0.9–1.0)	NS
Gender (male)	0.8 (0.4–1.8)	NS
Thyroid size	0.8 (0.5–1.2)	NS
fT4	0.9 (0.4–1.5)	NS
TRAb levels	1.0 (1.1–1.3)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; NS, not significant

At the time of diagnosis, no statistical difference was observed among REM and ABL for age, sex, fT4 levels and goiter size. Indeed, basal TRAb titer was significantly higher in ABL than in REM (87.2 ± 102.1 vs 42.4 ± 50.6 UI/L p<0.001). At the onset of hyperthyroidism the age of patients were not correlated to fT4 and TRAb levels (Pearson's correlation = 0.19, 0.17 respectively). At six months of follow up, all the 216 patients were still in treatment with antithyroid drugs. The whole duration of ATD therapy was significantly shorter in REM (17.5 ± 6.9 months) than in ABL patients (26.4 ± 11.1 months) (p<0.01). On the contrary, time lapsed from diagnosis to first withdrawal was sensible longer in patients who never relapsed (Group 1) than in those had at least one (Group 2 and Group 3) (Table 2) (p<0.001). Moreover, among these two groups, the subjects that at the end of follow-up arisen in remission group (Group 2), had a longer period of time from therapy withdrawal to first relapse than the Group 3 patients (p<0.05). Total duration of therapy, time lapsed from diagnosis to first therapy withdrawal and time lapsed from therapy withdrawal to first relapse and the decrease of TRAb levels after therapy withdrawal are reported in Table 2.

At the onset of hyperthyroidism mean fT4 level was 45.2 ± 18.9 pg/ml. Interestingly, logistic regression analysis showed that, among the selected variables available at the time of diagnosis, the only statistically significant predictor of the risk of first relapse after therapy withdrawal was fT4 levels (Table 3). Moreover, among REM patients initial fT4 levels were significantly lower in those who had never relapsed (Group 1) (p<0.001).

Predictors for remission or ablative treatment

Logistic regression analysis showed that, among the selected variables available at the time of diagnosis, the only statistically significant predictor of the following ablative treatment was TRAb titer (Table 4). Its prognostic value was evaluated by the ROC analysis which indicated a titer of 46.5 UI/L as the best cut off. In fact, an initial TRAb titer ≥46.5 UI/L identified patients who had never achieved remission with a sensitivity of 52%

Table 5. Predictive values for remission

	TRAb (IU/L)	Decrease TRAb (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Initial TRAb	46.5		52	78.0	52.0	76.9
TRAb at 6 M of follow up	30.7		52	80.0	53.2	78.7
Change in TRAb at 6 M of follow-up		52.3	55	79.1	55.0	73.0
Change in TRAb at therapy withdrawal		55.8	57	83.3	56.1	79.2

PPV = Positive predictive value; NPV = Negative predictive value.

Table 6. TRAb titer at the onset of hyperthyroidism and their fall of rate at 6 months of therapy

Initial TRAb (IU/L)	Decrease in TRAb (%)	REM n. patients (%)	ABL n. patients (%)
>46.5	>52.3	9 (9.9%)	24 (19.2%)
<46.5	<52.3	71 (77.2%)	60 (48%)
>46.5	<52.3	11 (12.1%)	41 (32.8%)
<46.5	>52.3	—	—

and a specificity of 78%.

TRAb titer at 3 and 6 months of ATD therapy and at therapy withdrawal were also available in all patients; only at 6 months of therapy and superimposable to basal titer, it was a significantly associated to the risk of thyroid ablation ($p<0.001$). At this time, a TRAb titer ≥30.7 UI/L identified patients who had never achieved remission with sensitivity of 52% and specificity of 80%. Moreover, also a percentage of TRAb fall rate at 6 months of therapy and at therapy withdrawal from the basal data were both significant predictors of a positive outcome ($p<0.001$) (Table 5).

TRAb at diagnosis and their fall rate percentage at six months of therapy are reported in Table 6.

Results show that no single parameter among TRAb, satisfactory identified a sub-set of patients who achieved long remission. Accordingly to our data, the best result in predicting long term remission is probably given by the presence of at least one of the two features evaluated at 6 months (TRAb titer and/or percentage of TRAb fall rate), with a sensitivity of 63% and specificity of 88%.

Discussion

Conservative therapy with ATD is the first choice treatment in Europe and it is proven to be effective in achieving euthyroidism in Graves' patients [3], even if long-term remission after therapy withdrawal is unsatisfying with relapse rates of 30–50% [9, 16–20]. However, if the great rate of relapse(s) may be related to TRAb levels and/or other parameters, such as gender, age, fT4 levels or goiter size is still controversial [13, 14, 20–23]. As known, the prevalence of Graves' patients is associated to gender, and, in accordance with this view, our subjects were predominant female (85.6% females, 24.4% males). Nevertheless, differently with previous reports [24, 25], any correlation between gender and relapse(s) was detected ($p = 0.973$). In a subgroup of women affected by GD, and after pregnancy, age resulted associated to relapse [26]; again, our data didn't show any correlation between age and this risk; probably it may due to different selection of patients.

High levels of fT4 at the onset of hyperthyroidism were already investigated as potential predictor of relapse(s) with discordant results [27–29]. In agreement with Weetman *et al.* [28], also our data showed that high levels of fT4 are significant associated to the risk of relapse(s) ($p<0.001$).

Clague *et al.* suggested a correlation between TRAb titers and fT4 levels at the time of diagnosis [30]. Our data didn't confirm this hypothesis; we believe, as already suggested by others [31, 32], that in spite of TRAb fundamental role in the etiopathogenesis of GD, many other biochemical signals produced by the immunological cells can modulate the synthesis and the excretion of thyroid hormone.

The distribution of goiter size among the Groups, at time of recruitment, was homogeneous. Recently, it has been suggested that goiter size could be a predictor of relapse(s) in GD [33, 34]: bigger is the volume, higher is the risk [33, 34], but any correlation between goiter size and relapse(s) rate of the disease was present in this study.

The major problem of GD, and the mainly end-point

of this resource, is the difficulty to find factors able to predict which patients are likely to achieve long-term remission after conservative medical therapy [7, 10, 13, 35].

Previous studies demonstrated an inverse correlation between patients' age and fT4 serum levels at the onset of hyperthyroidism [24, 25], patients' age and titer of TRAb at the time of diagnosis [24], patients' age and relapse risk after therapy withdrawal [36], suggesting that the autoimmune thyroid process was more prone to subside in patients older than 40 years. Our study didn't confirm this hypothesis: age distribution among Groups was casual and not correlated to fT4 levels, to TRAb titers and to the final outcome. We concluded that patients' age at the time of diagnosis couldn't predict the final outcome, but the mean age in our study was less than in previous studies (39.3 ± 13.0 years). It could be a consequence of an earlier diagnosis, probably due to our particularly attention to thyrotoxicosis as previously demonstrated [37, 38].

At the onset of hyperthyroidism no different fT4 levels were present among REM and ABL patients. Our study confirmed previous data [39, 40] obtained in adults and in children of the absence of influence of fT4 on the outcome.

As TRAb are considered the hall markers of GD [41, 42], their persistence in the blood of patients treated with ATD may indicate on going active disease. For this reason many investigators are focused on the possible role played by TRAb as predictors of GD outcome [10–13, 20, 43, 44].

In the onset of hyperthyroidism, TRAb levels resulted significant lower in Group1 than the others ($p<0.001$); moreover, their prognostic feature was confirmed during follow-up, which is already the longer never described (120 months). TRAb titer at diagnosis was strongly associated with the final outcome (sensitivity 52%, specificity 78%, $p<0.001$), in agreement with other authors [10–13].

With the aim to improve this results, we have evaluated the title of TRAb at 3 and 6 months of therapy, at therapy withdrawal, and also the percentage of their fall rate during ATD (at 6 months) and at its end. As already reported by Vitti *et al.* [9] only titer of TRAb at 6 months of ATD was associated to the outcome (sensitivity 52%, specificity 80%, $p<0.001$). Also a percentage of fall TRAb rate more than 50% at 6 months of therapy and at ATD withdrawal were eligible as predictors of outcome (sensitivity 55% and 57%; specificity 79.1% and 83.3%, respectively). No single parameter among TRAb, satisfactory identified a sub-set of patients who achieved long remission. Accordingly to our data, the best result in predicting long term remission is probably given by the presence of at least one of the two features evaluated at 6 months (TRAb titer and/or percentage of TRAb fall rate), with a sensitivity of 63% and specificity of 88%.

Finally, we have also evaluated if was present significant differences between total time of therapy and time lapsed from diagnosis to achieve euthyroidism among Groups.

The ABL subjects presented a longer whole duration of ATD than REM patients ($p<0.01$): obviously, this result is due to the fact that subjects with more relapses re-started therapy more times. Among patients that at the end of follow-up obtained completely remission, anti-thyroid drug therapy was shorter in patients without any relapse (Group 1) than the others (Group 2 and Group 3) ($p<0.05$); obviously, also this data is in line with the above explanation. On the contrary and quite surprisingly, time lapsed from diagnosis to first withdrawal (time to achieve euthyroidism) was significantly longer in Group 1 than Group 2 and Group3 ($p<0.001$).

We supposed that patients who achieved permanent remission without any relapse (Group 1) were affected by a "resistance" form of GD, which required a long-time therapy to achieve euthyroidism. According to our data and with previous investigations on the role of ATD on the responsive effects of thyroid tissue by TRAb modulation [20], it could be hypothesized that in patients with a "resistance" Graves' disease, it is more difficult to obtain euthyroidism; on the other end, if euthyroidism is achieve, there are more possibility to remain euthyroid. In fact, our data clearly showed that a longer-time treatment (more than 12 months) to achieve euthyroidism was associated with major decrease of TRAb, and also with better prognosis.

Moreover, supposing early relapses associated with a "greater" aggressiveness of GD, and subsequently with a worst prognosis, we have evaluated time lapsed from therapy withdrawal to first relapse (Table 2). According with our hypothesis, it resulted correlated with prognosis ($p<0.05$).

In conclusion, our data showed that at the time of diagnosis patients' age, gender, fT4 and size goiter are not associated to the final outcome.

TRAb titers evaluated both at the onset of hyperthy-

roidism that at 6 months of therapy or their rate of fall at 6 months and at ATD withdrawal are predictors of outcome. However, the presence of at least one, between titers of TRAb or their rate of fall at six months, resulted to be the best predictor of remission with the higher sensitivity and specificity.

References

1. Mckenna TJ (2001) Graves' disease. *Lancet* 357: 1793–1796.
2. Okamoto T, Iihara M, Obara T (2000) Management of hyperthyroidism due to Graves' and nodular disease. *World J Surg* 24: 957–961.
3. Feldt-Rasmussen U, Glinoer D, Orgiazzi J (1993). Reassessment of antithyroid drug therapy of Graves' disease. *Annu Rev Med* 44: 323–334.
4. Weetman AP (2000) Graves' Disease. *N Engl J Med* 343: 1236–1248.
5. Toft AD, Weetman AP (1998) Screening for agranulocytosis in patients treated with antithyroid drugs. *Clin Endocrinol (Oxf)* 49: 271–282.
6. Izumi Y, Takeoka K, Amino N (2005) Usefulness of the 2nd generation assay for anti-TSH receptor antibodies to differentiated relapse of Graves' thyrotoxicosis from development of painless thyroiditis after antithyroid drug treatment for Graves' disease. *Endocrine J* 52: 493–497.
7. Abraham P, Avenell A, Park CM, Watson WA, Bevan JS (2005). A systematic review of drug therapy for Graves' hyperthyroidism. *Eur J Endocrinol* 153: 489–498.
8. Levy EG (1997) Treatment of Graves' disease: The American Way. Baillieres *Clin Endocrinol Metab* 11: 585–595.
9. Vitti P, Rago T, Chiovato L, Pallini S, Santini F (1997) Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. *Thyroid* 7: 369–375.
10. Feldt-Rasmussen U, Schleusner H, Carayon P (1994) Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long-term remission after medical therapy of Graves' disease. *J Clin Endocrinol Metab* 78: 98–102.
11. Michelangeli V, Poon C (1998) The prognostic value of thyrotropin receptor antibody measurement in the early stages of treatment of Graves' disease with antithyroid drugs. *Thyroid* 8: 119–124.
12. Schleusener H, Schwander J, Fischer C, *et al.* (1989) Prospective multicentre study on the prediction of relapse after antithyroid drug treatment in patients with Graves' disease. *Acta Endocrinol (Copenh)* 120: 689–701.
13. Maugendre D, Massart C (2001) Clinical value of a new TSH binding inihibitory activity assay using human TSH receptors in the follow-up of antithyroid drug trated Graves' disease. Comparison with thyroid stimulating antibody bioassay. *Clin Endocrinol (Oxf)* 54: 89–96.
14. Davies TF, Roti E, Braverman LE, De Groot LJ (1998) Thyroid controversy-stimulating antibodies. *J Clin Endocrinol Metab* 83: 3777–3785.
15. Zweig MH, Campbell G (1993) Receiver-operating characteristic ROC plots: a fundamental evaluation tool in clinical medicine. *Clin Chem* 337: 1675–1681.
16. Hershman JM, Givens JR, Cassidy CE, Astwood EB (1966) Long-term outcome of hyperthyroidism treated with antithyroid drugs. *J Clin Endocrinol Metab* 26: 803–807.
17. Allannic H, Fauchet R, Orgiazzi J, Madec AM, Genetet B, Lorcy Y, Le Guerrier AM, Del ambre C, Derennes V (1990) Antithyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatement duration. *J Clin Endocrinol Metab* 70: 675–679.
18. Leech NJ, Dyan CM (1998) Controversies in the management of Graves' disease. *Clin Endocrinol (Oxf)* 49: 273–280.
19. Orgiazzi J, Madec AM (2002) Reduction of the risk of relapse after withdrawal of medical theraphy for Graves' disease. *Thyroid* 12: 849–853.
20. Carella C, Mazziotti G, Sorvillo F, Piscopo M, Cioffi M, Pilla P, Nersita R, Iorio S, Amato G, Braverman LE, Roti E (2006) Serum thyrotropin receptor antibodies concentrations in patients with Graves' disease bifore, at the end of methimazole treatement, and after drug withdrawal: evidence that the activity of thyrotropin receptor antibody and/or thyroid response modify during the observation period. *Thyroid* 16: 295–302.
21. Massart C, Orgiazzi J, Maugendre D (2001) Clinical validity of new commercial method for detection of TSH-receptor binding antibodies in sera from patients with Graves' disease treated with antithyroid drugs. *Clin Chim Acta* 304: 39–47.
22. Zimmermann-Belsing T, Nygaard B, Rasmussen AK, Feldt-Rasmussen U (2002) Use of the 2nd generation TRAK human assay did not improve prediction of relapse after antithyroid medical theraphy of Graves' disease. *Eur J Endocrinol* 146: 173–177.
23. Schott M, Morgenthaler NG, Fritzen R, Feldkamp J, Willenberg HS, Scherbaum WA, Seiissler J (2004) Levels of autoantibodies against human TSH receptor predict relapse of hyperthyroidism in Graves' disease.

Horm Metab Res 36: 92–96.
24. Nordyke RA, Gilbert FI, Harada ASM (1988) Graves' disease. Influence of age on clinical findings. *Arch Intern Med* 148: 623–631.
25. Aizawa T, Ishihiara M, Hashizume K, Takasu N, Yamada T (1989) Age-related changes of thyroid function and immunologic abnormalities in patients with hyperthyroidism due to Graves' disease. *J Am Geriatr Soc* 37: 944–948.
26. Benhaim Rochester D, Davies TF (2005) Increased risk of Graves' disease after pregnancy. *Thyroid* 15: 1287–1290.
27. Allahabadia A, Daykyn J, Holder RL (2000) Age and gender predict the outcome of teatment for Graves' hyperthyroidism. *J Clin Endocrinol Metab* 85: 1038–1042.
28. Weetman AP, Ratanachaiyavong S, Middleton GW (1986) Prediction of outcome in Graves' disease after carbimazole treatment. *Q J Med* 228: 409–419.
29. Martino E, Pinchera A, Capiferri E (1988) Dissociation of responsiveness to thyrotropin-releasing hormone and thyroid suppressibility following antithyroid drug therapy of hyperthyroidism. *J Clin Endocrinol Metab* 3: 543–549.
30. Clague R, Mukhtar ED, Pyle GA, *et al.* (1976) Thyroid stimulating immunoglobulins on the control of thyroid function. *J Clin Endocrol Metab* 43: 50–56.
31. Michico U, Satoshi I, Hideo S (2002) Thyroid specific T helper cell analysis by ELISPOT assay with thyrotropin receptor peptides. *Peptides* 23: 103–107.
32. Al-Humaidi MA (2000) Serum cytokines levels in Graves' disease. *Saudi Med J* 21: 639–644.
33. Bolanos F, Gonzalez-Ortiz M, Duron H, Sanchez C (2002) Remission of Graves' hyperthyroidism treated with methimazole. *Rev Invest Clin* 54: 307–310.
34. Bojarska-Szmygin A, Janicki K, Pietura R, Janicka L (2003) The usefulness of thyroid size and TSH receptor antibody (TRAb) determinations in predicting the effectiveness of tiamazole and I-131 treatment for Graves-Basedow's disease. *Ann Univ Mariae Curie Sklodowska [Med]* 58: 242–247.
35. Mevgendre D, Gate A, Campion L (1999) Antithyroid drugs and Graves' disease-prospective randomized assessment of long-term treatment. *Clin Endocrinol* 50: 127–132.
36. Yamada T, Aizawa T (1994) Age-related therapeutic response to antithyroi drug in patients with hyperthyroid Graves' disease. *J Am Geriatr Soc* 42: 513–516.
37. Cappelli C, Braga M, De Martino E, Castellano M, Gandossi E, Agosti B, Cumetti D, Pirola I, Mattanza C, Cherubini L, Agabiti Rosei E (2006) Outcome of patients surgically treated for various forms of hyperthyroidism with differentiated thyroid cancer: experience at an endocrine center in Italy. *Surg Today* 36: 125–130.
38. Vaiana R, Cappelli C, Perini P, Pinelli D, Camoni G, Farfaglia R, Balzano R, Braga M (1999) Hyperthyroidism and concurrent thyroid cancer. *Tumori* 85: 247–252.
39. Tajiri J, Noguchi S, Morita M, Tamaru M, Murakami N, Kato R (1991) Serum free triiodothyronine to free thyroxine ratio enables early prediction of the outcome of antithyroid drug theraphy in patients with Graves' hyperthyroidism. *Endocrinol Jpn* 38: 683–687.
40. Mussa GC, Corrias A, Silvestro L, Battan E, Mostert M, Mussa F, Pellegrino D (1999) Factors at onset predictive of lasting remission in pediatric patients with Graves' disease followed for at least three years. *J Pediatr Endocrinol Metab* 12: 537–541.
41. Akamizu T (2001) Antithyrotropin receptor antibody: an update. *Thyroid* 11: 1123–1134.
42. Paschke R, Ludgate M (1997) The thyrotropin receptor in thyroid diseases. *N Engl J Med* 337: 1675–1681.
43. Saiki Y, Ishihara T, Ikekubo K, Mori T (2005) Differences in TSH receptor binding and thyroid-stimulating properties between TSH and Graves' IgG. Slowly-acting TSH receptor antibody moieties in Graves' sera affect assay data. *Endocr J* 52: 45–55.
44. Okamoto Y, Tanigawa SI, Ishikawa K, Hamada N (2006) TSH receptor antybody measurement and prediction of remission in Graves' disease patients treated with minimum maintenance doses of antithyroid drugs. *Endocr J* 53: 467–472.