

## CLINICAL STUDY

# Effects of L-thyroxine administration, TSH-receptor antibodies and smoking on the risk of recurrence in Graves' hyperthyroidism treated with antithyroid drugs: a double-blind prospective randomized study

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## Abstract

**Objective:** In Graves' hyperthyroidism treated with antithyroid drugs (ATD), the overall relapse rate reaches 30–50% following ATD discontinuation. Conflicting results have previously been reported with regard to the usefulness of combining ATD with thyroxine (L-T<sub>4</sub>), and thereafter maintaining L-T<sub>4</sub> treatment after ATD withdrawal. Also, clinicians are in search of useful parameters to predict the risk of a recurrence of hyperthyroidism after ATD treatment.

**Design:** Eighty-two consecutive patients (70 women and 12 men; mean age 36 years) with a first episode of Graves' hyperthyroidism were investigated prospectively; they were treated with ATD for a total of 15 months, combined with L-T<sub>4</sub> (for at least 12 months) after they had reached euthyroidism, with the aim of maintaining serum TSH below 2.5 mU/l during the combined therapy. Following ATD discontinuation, the patients were randomly assigned (double-blind placebo-controlled trial) to taking 100 µg/day L-T<sub>4</sub> (vs placebo) for an additional year.

**Methods:** The following determinations were carried out at initial diagnosis: serum total T<sub>4</sub> and triiodothyronine (T<sub>3</sub>), free T<sub>4</sub> and T<sub>3</sub>, TSH, TSH-receptor antibodies (TSHR-Ab), thyroid scintigraphy and echography. During ATD treatment, serum free T<sub>4</sub> and T<sub>3</sub> and TSH concentrations were recorded after 1 (optional), 2, 4, 6, 9, 12 and 15 months, and echography at the end of ATD treatment. During the randomized trial, serum free T<sub>4</sub> and T<sub>3</sub> and TSH concentrations were checked every 3 months (or until a recurrence). TSHR-Ab titers were measured at initial diagnosis, after 6 months with ATD, and at the end of ATD treatment.

**Results:** L-T<sub>4</sub> administration, both during and after ATD treatment, did not improve the final outcome and recurrence rates were similar in placebo and L-T<sub>4</sub>-treated patients (30%). Two parameters were identified that might be useful to help predict recurrence risks after ATD: (i) positive TSHR-Ab (at the end of ATD treatment) was significantly associated with a greatly increased recurrence risk; and (ii) despite the relatively small number of patients who were smokers, regular cigarette smoking was shown, for the first time, to be significantly associated with an increased recurrence risk. Also, the deleterious effect of smoking was shown to manifest its impact independently of TSHR-Ab titers at the end of ATD treatment. Thus, compared with the overall 30% recurrence risk, non-smoking patients with a negative TSHR-Ab (at the end of ATD) had a lower (18%) recurrence risk; smoking patients with negative TSHR-Ab (at the end of ATD) had a 57% recurrence risk; non-smoking patients with positive TSHR-Ab (at the end of ATD) had a high (86%) recurrence risk; the recurrence risk was 100% in those few patients who both smoked and maintained a positive TSHR-Ab at the end of ATD treatment.

**Conclusions:** The present study confirmed that L-T<sub>4</sub> administration during and after ATD withdrawal did not improve remission rate. Two factors, namely positive TSHR-Ab at the end of ATD treatment and regular smoking habits may represent clinically useful (albeit not absolute) predictors of the risk of recurrence in patients with Graves' hyperthyroidism treated with ATD. However, due to the relatively small number of smoking patients in the present cohort, this conclusion needs to be confirmed by a larger study.

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## Introduction

In 1991, Hashizume *et al.* (1) reported significantly lower recurrence rates in patients with Graves' disease treated with antithyroid drugs (ATD) when thyroxine ( $L$ -T<sub>4</sub>) was given in combination with ATD and the patients maintained on  $L$ -T<sub>4</sub> for 3 years after ATD withdrawal. Other investigations, however, carried out later in both Japanese and Caucasian patients with Graves' hyperthyroidism, failed to confirm these promising results (2–4). The present study was undertaken before the latter studies were published. Our first aim was to reassess the usefulness of  $L$ -T<sub>4</sub> administered during and after ATD treatment in reducing the recurrence risk of hyperthyroidism in Graves' disease patients in Belgium. To this purpose, patients with a first episode of Graves' hyperthyroidism were treated with ATD for 15 months, combined with  $L$ -T<sub>4</sub> for 12 months at least, after regaining a euthyroid status. At the end of the combined treatment, all 82 patients were randomized into a double-blind prospective trial, and continued to take either  $L$ -T<sub>4</sub> or a placebo for an additional 12 months, during which period recurrence rates were assessed. Our second aim was to evaluate useful parameters that could be delineated during ATD treatment, to predict the risk of a recurrence following ATD withdrawal.

## Patients and methods

Eighty-two patients were recruited between October 1994 and December 1997 in 12 Belgian hospital centers with endocrinology referral clinics. Patients gave informed and signed consent to the study protocol, approved by the Ethical Committee of each participating hospital. For inclusion, patients fulfilled the following criteria: Caucasian origin, aged 20–55 years; first episode of Graves' hyperthyroidism, of recent onset and without prior treatment. Criteria of exclusion were: patients with ongoing pregnancy or desiring pregnancy; breast-feeding mothers; women in the child-bearing age without adequate contraception; known allergy/intolerance to drugs of the thionamide family; major illnesses or drug therapies influencing thyroid function parameters or interfering with their determination; severe ophthalmopathy corresponding to classes IV–VI of the NOSPECS American Thyroid Association classification (such patients were excluded to avoid the potential interference of steroid administration).

Initially, 178 hyperthyroid patients were recruited, but 96 were not included in the randomized trial, for one of the following reasons: loss of follow-up ( $n = 24$ ); patient's personal decision or randomization refusal ( $n = 16$ ); insufficient compliance ( $n = 14$ ); change in therapy ( $n = 9$ ); deviation from accepted protocol ( $n = 8$ ); pregnancy ( $n = 5$ ); miscellaneous ( $n = 20$ ).

## Study design

After confirmation of Graves' hyperthyroidism, the 82 patients participating in the randomized trial were first treated with ATD for a total of 15 months, 78 with methimazole (MMI) and four with propylthiouracil (PTU). When the patients reached euthyroidism, the maintenance dosage was adjusted to 15–30 mg/day MMI (or the equivalent for the few PTU-treated cases), and  $L$ -T<sub>4</sub> was given in combination with ATD. The daily  $L$ -T<sub>4</sub> dose was progressively adjusted to maintain euthyroidism, with serum thyrotropin (TSH) concentrations  $<2.5$  mU/l. Thus, total duration of ATD treatment was 15 months, with at least 12 months of combined treatment (Phase I of the study). At the end of Phase I, ATD were discontinued, and all 82 patients randomized for an additional period of 12 months, during which they received a fixed dose of  $L$ -T<sub>4</sub> (100  $\mu$ g/day) or placebo (Phase II of the study). Tablets containing either  $L$ -T<sub>4</sub> or placebo were specifically prepared for the present trial by Christiaens Pharma (Brussels, Belgium). During the entire study period, the patients were followed regularly (every 2 months during Phase I and every 3 months during Phase II).

**Recurrence** Recurrence during Phase II was defined as clinically recurring hyperthyroidism, confirmed by a suppressed TSH and elevated free hormone concentrations, with hyperthyroidism persisting after  $L$ -T<sub>4</sub> (or placebo) withdrawal. When a recurrence was suspected, the randomly assigned treatment was discontinued and patients withdrawn from the remainder of the study, but all cases continued to be monitored, even after treatment withdrawal. Remission was defined as clinical and biochemical evidence of euthyroidism, maintained throughout the 12 month period of randomization during Phase II.

## Laboratory determinations

The following determinations were carried out at initial diagnosis: serum total T<sub>4</sub> and tri-iodothyronine (T<sub>3</sub>), free T<sub>4</sub> and T<sub>3</sub>, TSH, thyroglobulin antibodies (TG-Ab), thyroperoxidase antibodies (TPO-Ab), TSH-receptor antibodies (TSHR-Ab), thyroid scintigraphy (using <sup>99m</sup>Tc or <sup>123</sup>I) and echography. During Phase I, serum free T<sub>4</sub>, free T<sub>3</sub> and TSH concentrations were recorded after 1 (optional), 2, 4, 6, 9, 12, and 15 months with ATD, with TSHR-Ab titers controlled at 6 and 15 months, and thyroid echography at 15 months. During Phase II, serum free T<sub>4</sub>, free T<sub>3</sub> and TSH concentrations were determined every 3 months (or until a recurrence was confirmed). TSHR-Ab titers were determined using a radio-receptor displacement assay, measuring the ability of patients' sera to inhibit the binding of radiolabeled TSH to solubilized porcine thyroid membranes (TRAK assay; Henning, Berlin, Germany).

**Table 1** Clinical characteristics and laboratory results at initial diagnosis of patients followed during Phase II. For clinical parameters, results are numbers of cases subsequently treated during Phase II with either L-T<sub>4</sub> or placebo who presented one of the recorded items (the relative frequency percentages in each group are shown in parenthesis).

	L-T <sub>4</sub> (n = 42)	Placebo (n = 40)
Presence of		
Goiter	31 (74%)	32 (80%)
Tachycardia	34 (81%)	33 (83%)
Tremor	29 (71%)	32 (80%)
Weight loss	29 (71%)	29 (73%)
Ophthalmopathy (grade I–III)*	11 (26%)	14 (35%)
Regular cigarette smokers	4 (10%)	7 (18%)
Thyroid function test (normal range)		
Total T <sub>4</sub> (50–150 nmol/l)	253 ± 15	257 ± 12
Total T <sub>3</sub> (1.4–3.2 nmol/l)	6.0 ± 0.5	6.3 ± 0.5
Total T <sub>3</sub> T <sub>4</sub> molar ratio (×10 <sup>3</sup> ) (10–22)	23.9 ± 1.5	24.9 ± 1.6
Free T <sub>4</sub> (10–25 pmol/l)	51 ± 3	49 ± 3
Free T <sub>3</sub> (3–11 pmol/l)	21 ± 2	18 ± 2

\* Based on the NOSPECS classification of the American Thyroid Association.

Differences between groups, analyzed by chi-square contingency tables, showed no statistical difference in relative frequencies. For laboratory data, results at diagnosis are presented as means ± s.e. in each group. Differences between groups, analyzed by one-way ANOVA, showed no statistical difference.

## Statistical analyses

Individual data were collected sequentially using a specifically designed software program (established by Michel Candeur from the Ecole de Santé Publique, Université Libre de Bruxelles). Statistical analysis was carried out using the SPSS program, as appropriate.

## Results

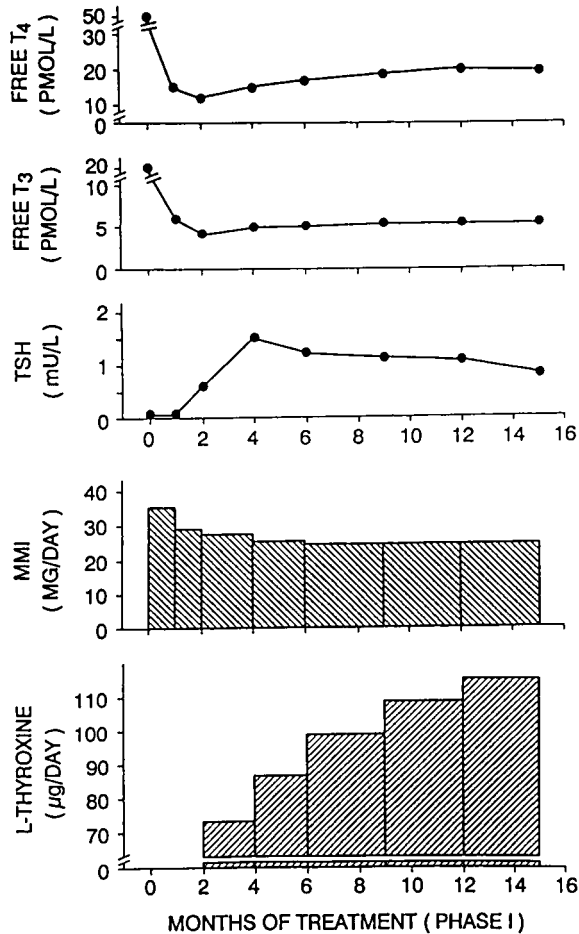
### Data at inclusion

As expected, the study group encompassed a majority of women ( $n = 70$ , 85%), compared with men ( $n = 12$ , 15%), with a mean age of 36 years (range 20–54 years), similar in both sexes. The main clinical characteristics and laboratory results at initial diagnosis are shown in Table 1. A diffuse goiter was present in 74–80% of the patients, of recent onset (<1 year) in 90% of these cases, with an elevated radionuclide uptake at scintigraphy. Tachycardia, tremor and weight loss were present in 71–83% of the patients, confirming overt thyrotoxicosis. Median weight loss was 6 kg (corresponding to 10% of body weight (BW)). Initial laboratory results showed markedly elevated serum total and free T<sub>4</sub> and T<sub>3</sub> concentrations, and molar ratios of serum total T<sub>3</sub>/T<sub>4</sub>; serum TSH was suppressed (<0.04 mU/l) in all patients. In Table 1, clinical data and laboratory results are listed separately for the groups receiving either L-T<sub>4</sub> or placebo during Phase II, to illustrate the absence of differences between the groups. With regard to thyroid immunity, TG-Ab, TPO-Ab and TSHR-Ab (titers >15 U/l) were initially positive in 51, 71 and 83% of the patients respectively.

### Phase I: antithyroid drug and L-T<sub>4</sub> treatment

A majority of patients (90%) received MMI, with only four patients given PTU initially and four patients switched from MMI to PTU, because of allergic side-effects. Initial MMI dosage ranged between 30 and 80 mg/day, with a mean of  $35 \pm 12$  (1 s.d.) mg/day (Fig. 1). During the first months, the MMI dosage was progressively reduced to a mean daily maintenance dosage of 25 mg, throughout Phase I. Figure 1 shows the pattern of free hormone concentrations during Phase I; serum free T<sub>4</sub> and T<sub>3</sub> reverted to normal within 1–2 months after starting ATD. Thereafter, serum free hormones remained within reference limits, due to the addition of progressively increasing L-T<sub>4</sub> doses, with a mean of 85, 100, 110 and 115 µg/day after 4, 6, 9 and 15 months respectively of the combined therapy. From not-detected values initially, median serum TSH increased to >0.40 mU/l in 50 and 70% of patients after 2 and 6 months respectively. Between 6 and 15 months in Phase I, the median serum TSH values ranged between 0.6 and 1.5 mU/l.

At the end of Phase I, serum TSH values were normal in 80%, while detectable but slightly subnormal in 20% of the cases. With regard to TSHR-Ab, antibody titers reverted to negative values in the majority of patients with initial positive TSHR-Ab. Antibody titers were negative at the end of Phase I in 88% of those patients with initially positive TSHR-Ab titers, but below 100 U/l; conversely, in most of the cases with initially positive TSHR-Ab titers but above 100 U/l, positive antibody titers tended to be maintained, even though the absolute TSHR-Ab titers frequently showed a decrease during ATD treatment.



**Figure 1** Pattern of changes in serum free T<sub>4</sub>, free T<sub>3</sub>, TSH concentrations and mean daily MMI and L-T<sub>4</sub> doses during combined ATD and L-T<sub>4</sub> treatment. The figure shows the mean results obtained in the 82 patients during Phase I.

### Phase II: the randomized trial after ATD treatment

At the end of Phase I, 42 patients (51%) were randomly assigned to receiving L-T<sub>4</sub> and 40 patients (49%) to placebo, for a period of 12 months. Both randomized groups were homogeneous with regard to the duration of prior ATD treatment: 457 vs 461 days (respectively for L-T<sub>4</sub> and placebo groups). Following ATD withdrawal, 51 patients remained in remission and 23 had a clear-cut recurrence of hyperthyroidism, namely 11

patients in the L-T<sub>4</sub>-treated and 12 in the placebo-treated group, yielding an overall recurrence rate of 28% (Table 2). Eight patients had a suppressed serum TSH, with only borderline elevated free T<sub>4</sub> (and normal free T<sub>3</sub>) concentrations. According to the protocol, these patients were withdrawn from the randomized trial, although not considered as 'truly' presenting a recurrence; after stopping medication, they remained euthyroid and it was shown later (after the random codes were broken) that seven out of eight cases had received L-T<sub>4</sub> during Phase II. In the statistical analysis, if the intermediate group was not included with the truly recurring patients, the recurrence rates were similar in placebo-treated and L-T<sub>4</sub>-treated patients (28 vs 34%). Alternatively, if the intermediate group was considered as truly recurring patients, the recurrence rate was even higher in L-T<sub>4</sub>-treated, compared with placebo-treated patients (45 vs 30%) (Table 2).

Figure 2 illustrates the pattern of changes in serum free T<sub>4</sub>, free T<sub>3</sub> and TSH concentrations in the group of patients who remained in remission. The figure shows that the main impact of L-T<sub>4</sub> (compared with placebo) was to significantly increase serum free T<sub>4</sub> (albeit still within the normal range) and, conversely, reduce serum TSH to near the lower limit of normality. Figure 3 compares serum free T<sub>4</sub> and T<sub>3</sub> concentrations in patients with a recurrence or remaining in remission, irrespective of the treatment given in Phase II. Patients who recurred showed an abrupt and marked rise in free hormone concentrations to thyrotoxic levels, with 50% of the recurrences occurring within 3 months and 75% within 6 months after ATD discontinuation; also, the rate and timing of recurrences were not influenced by the type of treatment given in Phase II.

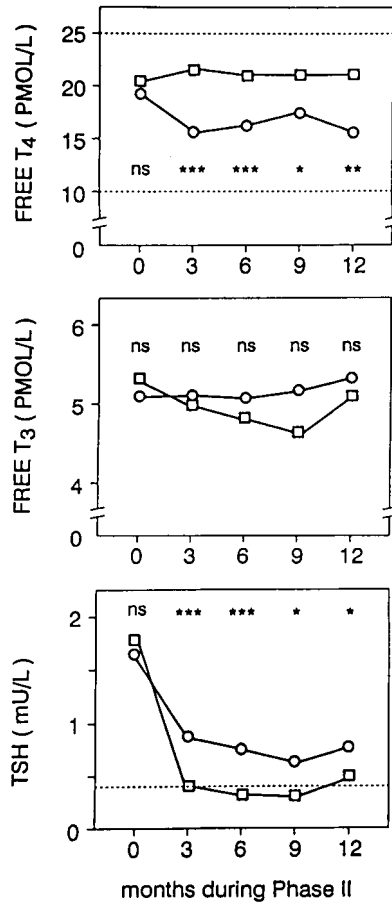
A series of variables were next evaluated, to assess whether they might be helpful in predicting remission/recurrence after ATD withdrawal. In these analyses, patients belonging to the 'intermediate' group (transient hyper-T<sub>4</sub>) were not included. Table 3 lists variables not found to be helpful in predicting recurrence; neither thyroid volume (both at initial diagnosis and at the end of Phase I) nor the initial hyperthyroidism's severity yielded significant predictive information.

Next, the impact of smoking and TSHR-Ab on remission and recurrence was analyzed. Concerning smoking, the number of regular cigarette smokers

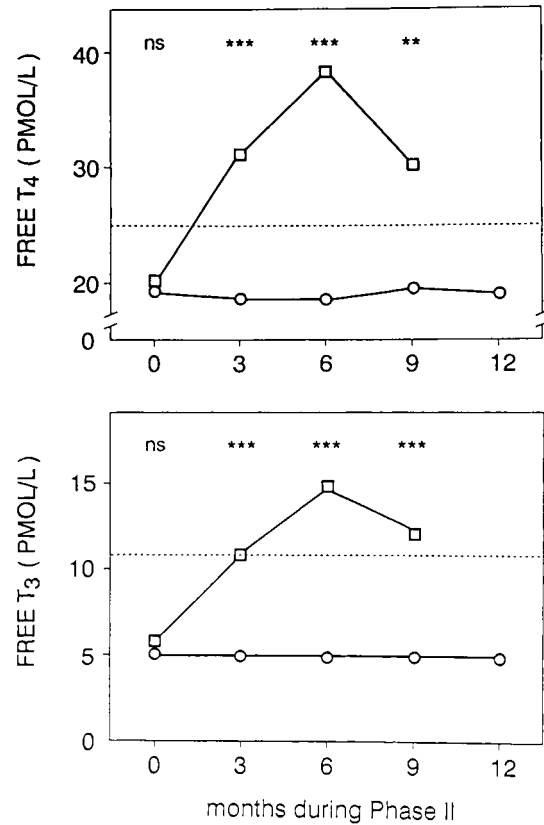
**Table 2** L-T<sub>4</sub> vs placebo administration after ATD withdrawal.

	Remission (n (%))	Recurrence (n (%))	Transient hyper-T <sub>4</sub> (n (%))	Total
Placebo	28 (34%)	11 (13%)	1 (1%)	40 (49%)
L-T <sub>4</sub>	23 (28%)	12 (15%)	7 (9%)	42 (51%)
Total	51 (62%)	23 (28%)	8 (10%)	82 (100%)

Contingency table analysis was used to compare the placebo and L-T<sub>4</sub>-treated groups in relation to remission and recurrence. Statistical analyses were performed on all 82 patients investigated (including the eight cases with only mild transient hyperthyroxinemia):  $\chi^2 = 2.023$ ;  $P = 0.16$ ; and on the 74 patients investigated, after excluding the eight cases with mild transient hyperthyroxinemia:  $\chi^2 = 0.098$ ;  $P = 0.75$ .



**Figure 2** Mean serum free T<sub>4</sub>, free T<sub>3</sub>, and TSH concentrations, at the end of Phase I and during Phase II in the group of patients who remained in remission after ATD discontinuation. Patients were randomized to receiving L-T<sub>4</sub> (n = 23) (□) or placebo (n = 28) (○) during Phase II. Statistical analysis was carried out, for each time point, using one-way ANOVA: \*\*\*P < 0.001, \*\*P < 0.01, \*P < 0.05, ns = not significant. The dotted horizontal lines indicate the normality range for serum free T<sub>4</sub> and the lower limit of normality for serum TSH.



**Figure 3** Mean serum free T<sub>4</sub> and free T<sub>3</sub> concentrations, at the end of Phase I and during Phase II, in the patients who had a recurrence (n = 23) (□) or remained in remission (n = 51) (○). Statistical analysis was carried out, for each time point, using one-way ANOVA (for symbols of P values, see the legend of Fig. 2). The dotted horizontal lines indicate the upper limit of normality for serum free T<sub>4</sub> and free T<sub>3</sub>.

**Table 3** Prediction of recurrence vs remission after ATD treatment. Results are presented as the relative percentages in groups with a recurrence or remaining in remission for qualitative variables, and P-values were calculated by  $\chi^2$  contingency tables. For the quantitative variables, mean values are listed for each group, and P-values were calculated by one-way ANOVA.

	Patients with		P-value
	Recurrence	Remission	
Season of onset of disease (fall and winter vs spring and summer)	48 vs 52%	45 vs 55%	1.00
Mean age at diagnosis	35.5 years	37.4 years	0.35
Ophthalmopathy at diagnosis (present vs absent)	35 vs 65%	29 vs 71%	0.85
Mean initial thyroid volume (at diagnosis)	23 ml	26 ml	0.48
Mean thyroid volume at the end of Phase I	23 ml	22 ml	0.89
Initial weight loss (percent of BW)	11.7%	11.5%	0.94
Severity of thyrotoxicosis at initial diagnosis			
Mean total T <sub>4</sub> (nmol/l)	259	253	0.77
Mean total T <sub>3</sub> (nmol/l)	5.75	6.11	0.61
Mean free T <sub>4</sub> (pmol/l)	48.8	50.1	0.78
Mean free T <sub>3</sub> (pmol/l)	20.1	19.6	0.85

**Table 4** Prediction of recurrence vs remission after ATD treatment: impact of TSHR-Ab positivity.

	TSHR-Ab		Percent positive
	Positive	Negative	
Patients remaining in remission after ATD withdrawal ( <i>n</i> = 51)			
At initial diagnosis	44	7	86
After 6 months with ATD	16	35	31
At the end of ATD	1	50	2
Patients with recurrence after ATD withdrawal ( <i>n</i> = 23)			
At initial diagnosis	20	3	87
After 6 months with ATD	11	12	48
At the end of ATD	9	14	39

was limited among the patients (among them, 20% smoked <10 cigarettes/day, 70% 10–25/day and 10% >25/day). Despite this limitation in numbers, the impact of smoking on the risk of recurrence was significant; 64% (7 out of 11) of the smokers had a relapse, while 75% (47 out of 63) of the non-smokers remained in remission ( $P = 0.012$ ;  $\chi^2 = 6.39$ , after Yates' correction). Also, our data bank indicated that the majority of patients who were regular smokers did not modify their daily cigarette consumption during the course of the study period.

Table 4 shows the results of TSHR-Ab analysis (initial positivity and changes in titers during Phase I) as a predictor of recurrence. At initial diagnosis, the frequency of positive TSHR-Ab was identical between the recurrence and remission groups. After 6 months with ATD, there was a slightly higher proportion of the recurring patients who maintained a positive TSHR-Ab, but the difference was not significant. The major difference for TSHR-Ab positivity was only observed at the end of Phase I; while 2% of the patients who remained in remission had a positive TSHR-Ab, 39% of the patients with a relapse had a positive TSHR-Ab (although their absolute titers may have decreased during ATD treatment). Maintaining a positive TSHR-Ab (at the end of ATD) was significantly associated with the risk of a relapse ( $P = 0.0001$ ;  $\chi^2 = 18.4$ ), yielding a 90% positive predictive value for positive TSHR-Ab and a 78% negative predictive value for negative TSHR-Ab. Finally and in order to validate statistically the effects of smoking and positive TSHR-Ab, a logistic regression analysis was performed. Results are given in Table 5, confirming both the significantly increased recurrence risk associated with smoking and positive TSHR-Ab, and indicating moreover that smoking and positive TSHR-Ab were independent factors in affecting the recurrence rates.

## Discussion

The present study confirms that L-T<sub>4</sub> administration, during and after ATD treatment, does not improve the

**Table 5** The impact of smoking and TSHR-Ab on the risk of recurrence: logistic regression analysis. Odds ratios, 95% confidence intervals (CI), and *P*-values were calculated for the effects of smoking and TSHR-Ab positivity at initial diagnosis, end of Phase I and during Phase II, compared with the non-smoking patients with negative TSHR-Ab, for whom odds ratios were set at 1. In the second step of the analysis, since the effects of a positive vs negative TSHR-Ab were shown to be non-discriminant at the time of the initial diagnosis, TSHR-Ab results were not included in the model (n.i.).

		Odds ratio	95% CI	<i>P</i> -value
At initial diagnosis				
Smoking	Yes	6.9	1.6–31	0.029
	No	1.0	–	–
TSHR-Ab	Positive	n.i.	n.i.	–
	Negative	n.i.	n.i.	–
At the end of ATD				
Smoking	Yes	7.0	1.4–36	0.019
	No	1.0	–	–
TSHR-Ab	Positive	27.7	3.0–256	0.003
	Negative	1.0	–	–
After ATD withdrawal				
Smoking	Yes	8.1	1.1–59	0.039
	No	1.0	–	–
TSHR-Ab	Positive	38.0	3.4–423	0.003
	Negative	1.0	–	–

outcome in Graves' hyperthyroidism, and presents evidence to indicate that smoking and a positive TSHR-Ab (at the end of ATD treatment) may represent useful criteria to help predict an increased recurrence risk after ATD withdrawal.

In Europe, and in contrast with the attitude prevailing in the USA, a majority of patients with a first episode of Graves' hyperthyroidism are treated with ATD, given usually for 12–18 months (5–9). Provided that the treatment is regularly taken, ATD are always effective, toxic side-effects usually remain minor (10, 11), and remission rates (within 1–5 years after withdrawal) reach 50–70% (12–16). Several studies have compared higher ATD (combined with thyroid hormones) vs lower (titrated) ATD dosage regimens in relation to remission rates; with only rare exceptions (17), most studies have not been able to show a significant advantage of regimens employing higher ATD doses (18–24).

In 1991, a Japanese prospective study reported that the recurrence rate was markedly reduced (to only 2%) when L-T<sub>4</sub> was combined with MMI and continued for 3 years after MMI withdrawal, compared with a recurrence rate of 35% observed in patients receiving only MMI (1). The authors postulated that higher TSH concentrations (when MMI was given alone) might have contributed to sustain antibody production to the TSH receptor, thereby explaining the differences in relapse rates. Such promising results were, however, not confirmed by other investigations reported later, from both Japan and elsewhere (2–4, 25). Since a combined regimen (ATD+ L-T<sub>4</sub>) is the preferred

therapeutic modality in Belgium, it was decided (back in 1995, before the follow-up studies were published) to reassess Hashizume's (1) results, using a slightly different protocol, in which all patients received L-T<sub>4</sub> combined with ATD, and were randomized to continuing L-T<sub>4</sub> (or placebo) after ATD withdrawal. The present results confirm those previously reported by McIver *et al.* (2), Rittmaster *et al.* (3, 25) and Tamai *et al.* (4); within 1 year after ATD withdrawal, 30% of the patients had a relapse, with no difference in relapses between placebo and L-T<sub>4</sub>-treated patients. Furthermore, not only was the final outcome not improved by L-T<sub>4</sub> administration but, in addition, the follow-up became more complicated in patients receiving L-T<sub>4</sub> after ATD withdrawal, because some of them displayed transiently moderate hyperthyroxinemia with serum TSH blunting, presumably as the result of adding 100 µg L-T<sub>4</sub>/day to patients who maintained 'autonomous' hormone production.

Several parameters have been investigated over the past years, in search of those that could help predict the risk of a recurrence; among other factors, glandular hypoechoogenicity or increased vascularization at ultrasonography (26, 27), a large initial goiter size with only minimal shrinkage during ATD (14), TRH testing (28), <sup>131</sup>I uptake suppression after L-T<sub>3</sub> administration (29), etc. Such factors, however, have been shown to be of little independent discriminative value (30–32).

Since Graves' disease is caused by auto-antibodies that stimulate thyroid function by interacting with the TSH receptor, several studies have examined the predictive value of TSHR-Ab changes, as a marker of disease activity. A meta-analysis of the impact of TSHR-Ab on long-term remission after ATD treatment, conclusively showed that a negative TSHR-Ab at the end of ATD therapy was associated with a high chance of maintaining remission, and a positive TSHR-Ab with a high relapse risk (33). Other studies later confirmed the prognostic value of TSHR-Ab becoming negative during ATD treatment (9, 30, 34). The present results are consistent with these earlier findings. While positive TSHR-Ab at diagnosis and after 6 months of ATD treatment were not useful predictors of recurrence, a positive TSHR-Ab at the end of ATD treatment was significantly associated with a high risk of recurrence; a negative TSHR-Ab predicted a 78% chance to maintain remission, while a positive TSHR-Ab predicted a 90% risk to recur during the year following ATD withdrawal (sensitivity 39%, specificity 98%).

Smoking constitutes a substantial risk factor in Graves' disease, particularly in thyroid-associated ophthalmopathy (35–40). To our knowledge, only one study has previously shown that smoking was associated with a higher risk of relapse, but the study was retrospective and TSHR-Ab was not measured (41). In the present work, despite the relatively small number of cases investigated, smoking conferred a significantly increased recurrence risk, confirmed by

**Table 6** The risk of recurrence after ATD withdrawal: TSHR-Ab determined at the end of ATD treatment.

TSHR-Ab	Smoking	Recurrence (%)
Negative	Negative	18
Negative	Positive	57
Positive	Negative	86
Positive	Positive	100

the logistic regression analysis, and was shown to have an impact independently of positive TSHR-Ab. The precise mechanisms underlying the deleterious effects of smoking on the thyroid gland remain unclear, but it is usually considered that smoking may directly stimulate goiter formation and thyroid function (40, 42, 43).

Until recently, the usefulness of measuring TSHR-Ab in the management of Graves' disease has remained a matter of debate (44). The results of the present study may perhaps lead to useful clinical predictions (synopsis in Table 6): (i) non-smoking patients with negative TSHR-Ab (at the end of ATD) had the lowest recurrence risk; (ii) smoking patients, also with negative TSHR-Ab, had a 3-fold higher recurrence risk (57 vs 18%); (iii) finally, patients with a positive TSHR-Ab (at the end of ATD) had the highest recurrence risk (86% in non-smokers and 100% in the few cases who also smoked). Since the study had not been designed specifically to investigate the impact of smoking, and due to the small number of smoking patients, the authors are aware that caution remains necessary before overemphasizing the importance of the present results, at least as long as these have not been confirmed by other studies encompassing a larger number of patients. However, the logistic regression analysis certainly tended to confirm that both TSHR-Ab positivity and smoking acted independently to increase recurrence risks. Applied to daily practice, the present findings constitute an encouragement to manage Graves' hyperthyroidism (especially in non-smoking patients) using a 12–18 month course of ATD, with a high chance to maintain remission, provided that TSHR-Ab titers are negative at the end of ATD treatment. The present findings also provide an encouragement to: (i) more strongly insist that patients refrain from smoking, although it remains to be shown that cessation of smoking after diagnosing Graves' disease can still modify the inherent risk of recurrence; (ii) perhaps, maintain ATD treatment for longer periods, when TSHR-Ab remains positive; and finally (iii) probably convince smoking patients to benefit from a radical treatment of the disease, particularly when TSHR-Ab remained positive after ATD treatment.

In conclusion, the present prospective study showed that L-T<sub>4</sub> administration (during and after ATD) did not improve the recurrence risk, hence confirming earlier studies. The study also showed that a combination of

parameters, namely a positive TSHR-Ab at the end of ATD treatment and smoking, provided clinically useful (albeit not absolute) predictors of the risk of recurrence in patients with Graves' hyperthyroidism treated with ATD.

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