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# Prediction of Remission or Relapse for Graves' Hyperthyroidism by the Combined Determination of Stimulating, Blocking and Binding TSH-Receptor Antibodies after the Withdrawal of Antithyroid Drug Treatment



**Abstract**

The most likely reasons for the low predictive value of TSH-receptor antibodies (TRAbs) determinations in previous investigations are the biological heterogeneity of TRAbs and changes of the different stimulating (TSAb) or blocking (TSBAb) antibody bioactivities of TRAbs during the course of Graves' disease (GD), which have not been taken into account in most previous studies. Furthermore, in a recent study it has been demonstrated that the decline of TRAb values detected with highly sensitive hTBII or TSAB assays is not useful in evaluating remission or relapse of GD at the end of antithyroid drug treatment (ATDT). In order to make a thorough investigation of the predictive values of all different TRAb qualities for the recurrence for GD after the withdrawal, we investigated hTBII, TSAbs and TSBAbs in 54 consecutive patients with GD at the end of ATDT and 12 – 13.5 months after stopping ATDT. Using the TRAb values at the time of reinvestigation in a model, recurrence for GD was better predicted compared to the determination at the time of withdrawal of ATDT. Furthermore, using this model, the combined determination of hTBII, TSAbs, and TSBAbs revealed the highest level of significance for the prediction of remission or relapse of GD ($OR = 15$; $p < 0.0001$) compared to the detection of hTBII, TSAbs and TSBAbs alone. Therefore, significant changes of TSAbs after the end of ATDT and the biological heterogeneity of TRAb define the conditions for predicting remission or relapse of GD after ATDT by TRAb determinations. Consequently, our results suggest that the prediction of the individual course of GD can only be improved by combined determinations of all TRAb qualities (hTBII, TSAbs and TSBAbs) after the end of ATDT.

**Key words**
Thyroid Antibodies · Graves' Disease · Remission · Relapse



## Introduction

In Europe and the United States, a course of antithyroid drug treatment (ATDT) with or without $T_4$ replacement lasting 12 to 18 months is the first choice in treating Graves' hyperthyroidism [1 – 3]. It has been demonstrated that most relapses following ATDT occur within the first 12 months [3 – 8] regardless of the dosage of ATDT [3, 9 – 11]. This may partly reflect the natural history of the disease [3]. Various parameters have been tested for their ability to predict the clinical course of Graves' disease (GD) patients after ATDT. Remission in patients with slight goitre and low levels of TSH-receptor antibodies (TRAbs) is more frequent (43 %) than in patients with large goitre and high titre of TRAb [8]. Two prospective randomised studies and a meta-analysis of 18 studies confirmed the highest association between 70 % increased chances of long-term remission and the absence of TRAbs at the end of ATDT as compared with, for example, $T_3$ suppressibility of the thyroid gland, serum concentration of TSH, and TRH stimulation test [4, 6, 7]. However, the determination of thyrotropin binding inhibiting immunoglobulins (TBII) alone or in combination with thyroid stimulating antibodies (TSAbs) cannot predict relapse or remission in an individual patient when detected at the end of ATDT of GD [4, 6, 7]. Furthermore, it has been demonstrated that the determination of TRAbs prior to or

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at the beginning of ATDT has no prognostic value in predicting Graves hyperthyroidism relapse [7,12]. Moreover, TBII and TSAb courses during ATDT vary [22]. Therefore, TRAb values determined before ATDT are not useful in predicting remission or relapse after ATDT.

Transitions from TSAbs to thyrotropin stimulation blocking antibodies (TSBAbs) and *vice versa* have been documented [13,14]. Decreasing TSAb activities and transitions from TSAbs to TSBAbs have been discussed as possible reasons for remission of Graves' disease after ATDT [3,13–17]. These transitions are not always detectable in a TBII assay, alone or in combination with TSAb determination. We have detected TSBAbs in 34 of 86 TSAb-negative sera of patients with Graves' disease during or after ATDT [18]. Furthermore, we have demonstrated that TSH displacement by TRAbs and stimulation or blocking of the TSH-receptor by TRAbs are separate functions that do not need to occur together [19]. These results are in accordance with reports describing TRAbs that bind but do not stimulate the TSH receptor [20,21]. Furthermore, differences between changes in TBII and TSAbs were identified during and after ATDT [22]. Therefore, the prediction of the individual course of GD after ATDT can most likely only be improved by a repeated and combined highly sensitive determination of hTBII, TSAbs and TSBAbs after the withdrawal of ATDT.

To investigate the prognostic value of hTBII, TSAb and TSBAb determination and the combined determination of these TRAbs for the prediction of remission or relapse after ATDT, we determined hTBII, TSAb and TSBAb values in 54 consecutive patients with GD at the end of ATDT. Also, all patients were reinvestigated for all TRAbs and for remission or relapse of Graves' hyperthyroidism after the withdrawal of ATDT.





## Patients and Methods

### Patients

54 consecutive patients with Graves' hyperthyroidism (43 females, 11 males) were investigated. The diagnosis of GD based on clinical and laboratory criteria, including TSH, $fT_3$, $fT_4$, TBII and anti-TPO-antibodies, scintiscan and ultrasound. All patients were treated with methimazole (< 40 mg/d with or without $T_4$ replacement) for over 12 months. It has been demonstrated that an ATDT of more than 18 months has no influence on the relapse rate of Graves' hyperthyroidism [23]. In our study, the duration of ATDT was longer than 12 months. Therefore possible differences in the duration of ATDT between patients who achieved remission and patients who relapsed most likely did not influence the relapse rates determined in this study. Serum samples were prospectively obtained for measuring hTBII, TSAB and TSBAB at the end of ATDT, when patients were euthyroid. None of these 54 patients were treated with radioiodine or surgery. After the end of ATDT, all patients were reinvestigated (Fig. **1**), including TSH, $fT_3$, $fT_4$, and ultrasound. Relapse was diagnosed by elevated $fT_4$ and supressed TSH levels (ultrasensitive assay) as previously described [5–12]. Patients were divided into group A, who achieved remission of Graves' hyperthyroidism (n = 24) and group B, who suffered from relapse of Graves' hyperthyroidism (n = 30) after the withdrawal of ATDT. Patients in group A were investigated for TRAbs on average 12 months (range: 5–24) after withdrawal of ATDT, whereas the patients of group B were investigated for TRAb at the time of relapse of Graves' hyperthyroidism, on average 13.5 months (range: 3–26) after withdrawal of ATDT (Fig. **1**). The observation times in both groups were not significantly different (p = 0.896) as determined by the Mann-Whitney U-test.

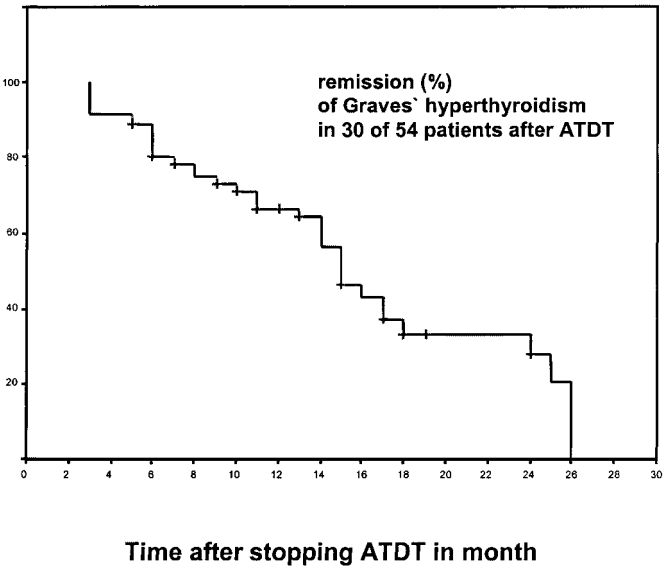


Fig. **1** Time to treatment failure of 30 patients who suffered from relapse after antithyroid drug treatment.

### hTBII assay

It was recently reported that the recombinant human TSH receptor in a new TBII assay technique (DYNOTEST TRAKhuman, Brahms, Berlin, Germany) improve the sensitivity and specificity for the detection of TRAb in Graves' disease patients to 98.8% or 99.6%, respectively [24]. Therefore, all samples were analysed in this highly sensitive hTBII assay, performed according to the manufacturer's instructions as previously described [19].

### TSAB and TSBAB assay

The TSAB and TSBAB assay were performed using JP26 and JP02 cells as previously described [18,19]. The intraassay and interassay variance was lower than 10% and 15%, respectively. All assays were performed in duplicate in at least two separate experiments. Results for TSAbs and TSBAbs were calculated as follows:

*Stimulation index*: TSAbs (%) = 100 × JP26 (cAMP patient/cAMP control)/JP02 (cAMP patient/cAMP control)

*Inhibition index:* TSBAbs (%) = 100 × (1 – JP26 [cAMP patient TSH/cAMP control TSH]/JP02 [cAMP patient TSH/cAMP control TSH]).

### Statistical analysis

Time-to-treatment failure (relapse of Graves' hyperthyroidism after the end of ATDT) was documented using a Kaplan-Meier curve. Most of the previous investigations of TRAbs for the prediction of remission or relapse were calculated by univariate analysis [4,6,7]. However, it is well known that multivariate analysis have a higher statistical power than univariate analysis, especially when comparing different predicting factors. Due to the reported differences between TBII and TSAb and TSBAb values, which imply that TBII activity and stimulating or blocking

Table **1** Univariate analysis of the relapse-predictive value of the determination of TSH-receptor antibodies at the end of antithyroid drug treatment

| | *hT BII* | | | *TS AB* | | | *TS BAB* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Positive* | *Negative* | *P* | *Postive* | *Negative* | *p* | *Positive* | *Negative* | *P* |
| Relapse | 24 | 6 | 0.04** | 17 | 13 | 0.9 | 5 | 25 | 0.5 |
| Remission | 11 | 13 | | 13 | 11 | | 6 | 18 | |

** OR = 3.

Table **2** Multivariate analysis of the relapse-predictive value of the determination of TSH-receptor antibodies at the end of antithyroid drug treatment and at time x

| | *At the end of ATDT* | | *At time x* | |
|---|---|---|---|---|
| | *p* | *OR* | *OR* | *p* |
| hTBII | 0.1 | 3 | 0.1 | 4 |
| TSAB | 0.3 | 0.5 | 0.01 | 26 |
| TSBAB | 0.4 | 0.5 | 0.03 | 8 |
| hTBII + TSAB | 0.2 | 2.7 | 0.0004 | 10 |
| TSAB + TSBAB | 0.5 | 0.6 | 0.001 | 15 |
| hTBII + TSAB + TSBAB | 0.5 | 1.8 | 0.0001 | 15 |

activity do not always occur together in one serum sample [19], we evaluated the predictive values for relapse of Graves' hyperthyroidism at the end of ATDT for all TRAbs using univariate and multivariate analysis. Furthermore, changes in hTBII, TSAb or TSBAb values between the end of ATDT and time of reinvestigation for remission or relapse were computed by McNemar's test.

To investigate the predictive value of possible changes of TRAb values between the end of ATDT and the time of reinvestigation, we established a model for the possible prediction of remission or relapse of Graves' hyperthyroidism after stopping ATDT. This model is based on the hypothesis that the TRAb values change after the end of ATDT. Also, our model assumes that TRAb values, which are detectable at the time of remission or relapse, can already be detected at time x (several weeks before the relapse or remission occurs) without further changes in the TRAb profile until the relapse occurs. Due to changes in TRAb values after the end of ATDT, the determination of TRAbs at time x could have a higher prognostic significance than the detection of TRAbs at the end of ATDT. Therefore, all TRAb values at the time of remission or relapse were analysed using our model in univariate and multivariate analysis for their ability to predict remission or relapse of Graves' hyperthyroidism at time x. The predictive value for remission or relapse of Graves' hyperthyroidism after ATDT was quantified by the Odds ratio (OR); p-values of less than 0.05 were considered as statistically significant. Data were analysed with SPSS for Windows (realised 8.0.0).

## Results

### The predictive values for remission or relapse of hTBII, TSAb or TSBAb determination at the end of antithyroid drug treatment

30 of 54 (55%) patients with GD relapsed within 26 months after stopping ATDT, whereas 24 of 54 (45%) patients were in remission at the time of reinvestigation after the end of ATDT (Fig. **1**). At the end of ATDT, positive TRAb values were detectable in 24 (80%), 17 (57%) and 5 (17%) of 30 patients who relapsed using the hTBII, the TSAB and the TSBAB assay respectively. However, in patients with remission, TRAbs were detectable in 11 (46%), 13 (54%) and 6 (25%) of these 24 patients in the hTBII, TSAb, and TSBAb assay, respectively. At the end of ATDT, only TRAbs detectable in the hTBII-assay revealed predictive values for remission or relapse (OR = 3; p = 0.04) by univariate analysis (Table **1**) as well as by the multivariate analysis (OR = 3; p = 0.1, Table **2**) with a sensitivity of 65% and a specificity of 65% respectively (data not shown).

### Changes of TRAb values between the end of ATDT and the time of reinvestigation for relapse or remission of Graves' hyperthyroidism

Between 12 and 13.5 months after the end of ATDT, all patients were reinvestigated for remission or relapse, respectively (Fig. **1**). At this time, positive TRAb values were detectable in 21 (70%), 12 (40%) and 8 (27%) of the 30 patients with relapse using the hTBII, the TSAb, and TSBAb assay, respectively. In contrast, positive TRAb values were detectable in 8 (33%), 1 (4%) and 2 (8%) of these 24 patients using the hTBII, the TSAb and the TSBAb assays, respectively, in patients who achieved remission. In patients who achieved remission, significant changes of positive TRAb values between the end of ATDT and the time of reinvestigation were

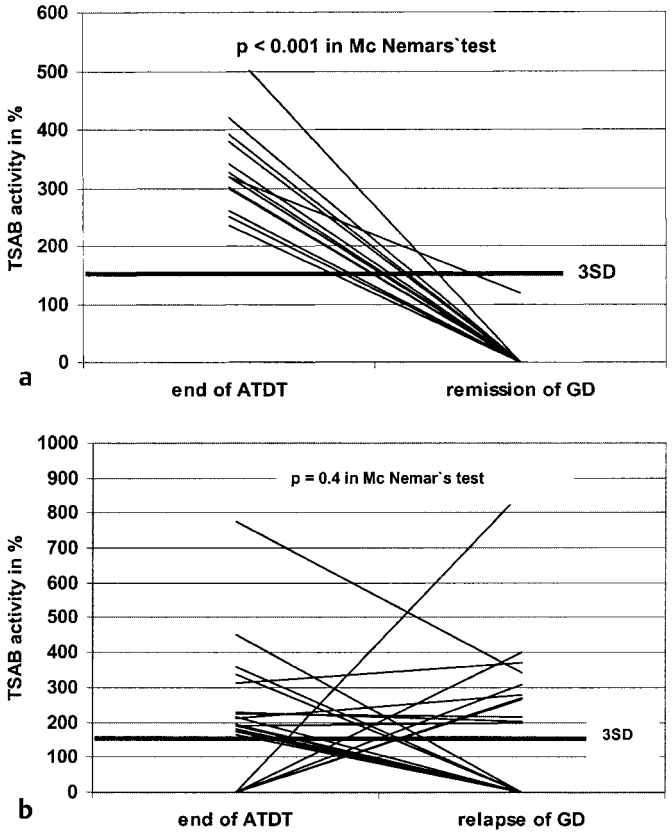


Fig. **2** **a** Significant changes of TSAB activity in 24 patients (loss of TSAB activity in 12 of 13) with Graves' disease who achieved remission after the end of antithyroid drug treatment. **b** No significant changes of TSAB activity in 30 patients with Graves' disease who suffered from relapse after the end of antithyroid drug treatment.





only detectable in the TSAb assay ($p < 0.0001$). These significant changes in TSAB activity in patients with remission between the end of ATDT and the time of reinvestigation are characterised by the loss of TSAb in 12 of 13 patients. One of the 13 sera was borderline positive for TSAbs ($3SD > x > 2SD$) at the time of reinvestigation (Fig. **2a**). After the end of ATDT, the patients who relapsed showed neither significant changes of TSAb ($p = 0.359$) or TBII or TSBAb values during the observation interval.

### The predictive values for remission or relapse of hTBII, TSAB or TSBAB determination after the end of antithyroid drug treatment using a statistic model

To further investigate the significant changes of TSAB after the end of ATDT in patients with remission (Fig. **2a**), we established a model to calculate the possible prediction of remission or relapse of Graves' hyperthyroidism after stopping ATDT. We analysed the detected hTBII, TSAb and TSBAb values at the time of remission or relapse in our model by multivariate analysis for their predictive value for relapse of Graves' hyperthyroidism at time x. In this multivariate analysis, the determination of TSAbs ($OR = 26$, $p = 0.01$) showed a significantly higher prognostic significance for relapse than hTBII ($OR = 4$; $p = 0.1$) or TSBAbs ($OR = 8$; $p = 0.03$), respectively (Table **2**). The reported heterogeneity of TRAbs suggests that the combined determination of hTBII, TSAb and TSBAb values during the course of GD could improve the prediction of the individual course of GD after ATDT. Therefore, we analysed the cumulative predictive value of the combined hTBII, TSAb and TSBAb determination at the end of ATDT and at time x after ATDT. The combined determination of the hTBII, TSAb and the TSBAb values could not predict relapse ($OR = 1.8$; $p = 0.5$) at the end of ATDT (Table **2**). In contrast, on the basis of statistical significance determined as the p-value, the combined results of all three assays (hTBII, TSAbs and TSBAbs) showed a higher predictive value for relapse ($OR = 15$; $p = 0.0001$) than the combined determination of TSAbs and TSBAbs ($OR = 15$; $p = 0.001$) or the combined determination of hTBII and TSAbs ($OR = 10$; $p = 0.0004$), or the determination of TSAbs ($OR = 26$; $p = 0.01$) alone (Table **2**).

## Discussion

The aim of this study was to investigate the predictive value for remission or relapse for GD by the highly sensitive hTBII, TSAb, or TSBAb determination after the withdrawal of ATDT. Therefore, we analyzed these TRAb values in 54 consecutive patients with GD at the end and 12 – 13.5 months after stopping ATDT.

At the end of ATDT, only TRAbs detected in the hTBII assay showed a positive predictive value for relapse of Graves' hyperthyroidism, whereas TSAb and TSBAb determination revealed no prognostic significance in our study (Table **1**). The most likely reason for this different predictive value of the hTBII and the TSAb values might be that the decline of TBII and TSAb values during ATDT could differ for some patients, as previously reported [12]. Moreover, in a previous study on patients with GD after antithyroid drug treatment, we demonstrated that TSH displacement by TRAbs and TBII and stimulation or blocking activity by TRAbs are different functions that do not need to occur at the same time [19].

In all previous studies, the ability of TBII determinations to predict remission or relapse of GD was only investigated at the end of ATDT [4, 6, 7]. However, patients with positive TBII or TSAb values at the end of ATDT who did not relapse, or patients with relapse despite non-detectable TBII or TSAb values have been identified in all previous studies [4, 6, 7] as well as in our study. These findings [4, 6, 7] demonstrate that an individual prediction of remission or relapse for patients with Graves' hyperthyroidism after ATDT is not possible by a single TRAb determination at the end of ATDT. Furthermore, it has been demonstrated that the decline of TRAb values after a term of 18 months ATDT could not predict remission or relapse of GD after stopping ATDT [12], as suggested by others [6]. Moreover, in a recent study, it has been suggested that patients with detectable hTBII at time of withdrawal of ATDT who did not relapse or patients with relapse despite non-detectable TBII or TSAb values were "misclassified" in these highly sensitive hTBII and TSAb assays [12]. Therefore, the authors argued that the cut-off value of the hTBII assay used to assess the risk for recurrence for GD might be different from the cut-off value used for diagnostic and differential diagnosis purposes as suggested by [25]. Using a higher cut-off [> 5 IU/ml in the hTBII assay or 300 % in the TSAB assay] than in the routine assay, only one patient was still positive for high TBII in population in this study [12]. In 24 of 30 patients (80 %) who relapsed, hTBII activity was detectable at the end of ATDT. These findings are in accordance with positive TBII values at the end of ATDT in 93 of 189 (49 %) patients who relapsed, as demonstrated in a previous

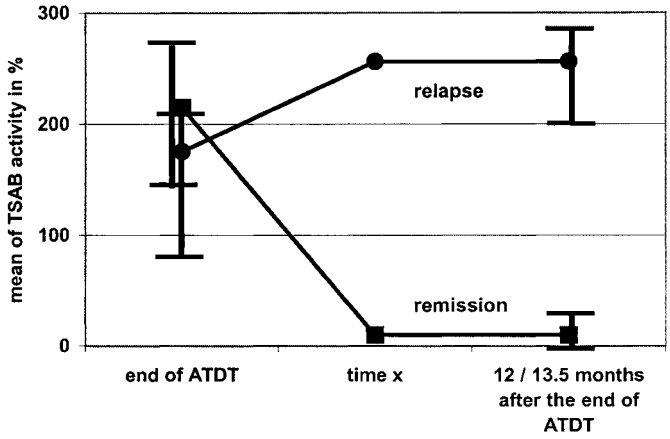


Fig. **3** Mean TSAb values at the end of ATDT and at the hypothetic time x for 54 patients with Graves' disease.

prospective study using a porcine TBII assay [7]. These findings demonstrate that the hTBII assay's higher sensitivity compared to the porcine TBII assay does not result in a loss of sensitivity to predict remission or relapse after ATDT.

However, the recent study demonstrated that 15% of those patients with detectable hTBII at the time of ATDT cessation lost their hTBII after the withdrawal of ATDT [12]. Moreover, some patients with detectable hTBII at the time of relapse were always negative for hTBII few months before [12]. Therefore, we hypothesised that further changes in TRAb values after the withdrawal of ATDT are likely to influence the individual course of GD. To investigate the predictive value of TRAb changes after the end of ATDT further, we also determined the TRAbs in the hTBII, TSAb and TSBAb assay at the time of reinvestigation after stopping ATDT. In patients who achieved remission, significant changes in TRAb values between the end of ATDT and the time of reinvestigation were only detected for TSAb assay results ($p < 0.001$ McNemar's' test). 12 of 13 patients with remission showed a loss of TSAb activity; one of these 13 patients was only borderline TSAb-positive at time of reinvestigation (Fig. **2a**). In contrast, no significant changes in TRAb values were detectable in patients with a relapse of Graves' hyperthyroidism. These significant changes of TSAB values in our study in patients with remission suggest that a prediction of relapse or remission could only be improved by further TRAb determinations after stopping ATDT.

Therefore, we tried to determine if these TRAb changes after the end of ATDT could be used to predict relapse or remission of GD. To be able to predict the course of GD, it should be possible to identify the TRAb changes after ATDT at an earlier time point. Thus, we established a model for the possible prediction of remission or relapse of Graves' hyperthyroidism after stopping ATDT. Our model is based on the hypothesis that TRAb values change after the end of ATDT. Our results on TSAb changes in patients who achieved remission (Fig. **2a**) support this hypothesis. Furthermore, our model assumes that TRAb values, which are detectable at the time of remission or relapse, can already be detected at time x (several weeks before the relapse or remission occurs) without further changes of the TRAb profile until the relapse occurs. Due to changes in TRAb values after the end of ATDT, the determination of TRAbs at time x could have a higher prognostic significance than the detection of TRAbs at the end of ATDT (Fig. **3**). In a multivariate analysis based on our model, the determination of TRAb values at time x has a higher prognostic value for relapse than its determination at the end of ATDT (Table **2**). The determination of TSAbs (OR = 26; $p = 0.01$) showed a significantly higher prognostic value for relapse than hTBII (OR = 4; $p = 0.1$) or TSBAB (OR = 8; $p = 0.03$) respectively (Table **2**). The higher prognostic value of the TRAb determination at time x compared to the end of ATDT, especially for the TSAB determination, is most likely due to the previously reported changes of TRAb during the course of GD [13,22,26] and the significant changes of the TSAB activity in those patients who achieved remission after the end of ATDT in our study.

However, we demonstrated in a previous study that TSAbs or TSBAbs stimulating or blocking the TSH receptor is possible without inhibition of $^{125}$I-bTSH binding [19]. In this previous study [19], possible confounding factors of the assay comparison, such as different assay conditions, intra- and interassay variability, and different TSH receptor species, were excluded. Because of the reported biological heterogeneity of TRAbs and the transitions from TSAbs to TSBAbs and *vice versa*, which are not always detectable in a TBII assay or by the combined determination of TSAbs and TBII [19,21], combined hTBII, TSAb and TSBAb determination seems to be a more comprehensive reflection of the activity variations of the autoimmune process and the variable production of TRAb by B lymphocytes in GD than the determination of either hTBII, TSAB or TSBAB alone.

At the end of ATDT, the combined results of all three assays (TRAK-human, TSAb and TSBAb) showed no cumulative predictive value in univariate analysis (OR = 1.8; $p = 0.5$). In contrast, at time x, the combined results of all three assays (TRAK-human, TSAb and TSBAb) showed the highest predictive value for relapse (OR = 15; $p < 0.0001$), even higher than the combined determination of TRAK-human and TSAb (OR = 10; $p = 0.0004$) or the combined determination of TSAbs and TSBAbs (OR = 15; $p = 0.001$) or the determination of either TBII or TSAbs or TSBAbs alone (Table **2**). This can most likely be explained by the combination of significant TSAb changes and the changes of different TRAb qualities that do not need occur together during the course of GD in our patients (Fig. **2a**) and reported by others [22] respectively.

However, we are aware that our retrospective pilot study has certain limitations:

Although our results were statistically significant, the population of our pilot study was smaller than in previous prospective studies. Also, whether the higher prognostic significance of the combined TRAb determination at time x after the end of ATDT is to have clinical consequences as suggested in our model will depend on the time interval between time x and the time of relapse. Nevertheless, our findings demonstrate that TRAb changes during the ATDT, and especially after the end of ATDT, and the reported biological heterogeneity of TSH receptor antibodies [19,22] are likely to define the conditions for predicting remission or relapse of GD after ATDT. This has not been taken into account in all previous studies. Therefore, our model suggests a new concept in solving the clinical problem of prediction of relapse or remission of Graves' hyperthyroidism after stopping ATDT. However, a prospective randomised study will be neces-

sary to clarify the possibility of predicting remission or relapse of GD for the individual patient by the combined determination of all TRAb qualities after the end of ATDT as suggested by the results obtained with our model.


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