Usefulness of Measuring Thyroid Stimulating Antibody at the Time of Antithyroid Drug Withdrawal for Predicting Relapse of Graves Disease

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Background: Hyperthyroidism relapse in Graves disease after antithyroid drug (ATD) withdrawal is common; however, measuring the thyrotropin receptor antibody (TRAb) at ATD withdrawal in order to predict outcomes is controversial. This study compared measurement of thyroid stimulatory antibody (TSAb) and thyrotropin-binding inhibitory immunoglobulin (TBII) at ATD withdrawal to predict relapse.

Methods: This retrospective study enrolled patients with Graves disease who were treated with ATDs and whose serum thyroid-stimulating hormone levels were normal after receiving low-dose ATDs. ATD therapy was stopped irrespective of TRAb positivity after an additional 6 months of receiving the minimum dose of ATD therapy. Patients were followed using thyroid function tests and TSAb (TSAb group; n=35) or TBII (TBII group; n=39) every 3 to 6 months for 2 years after ATD withdrawal.

Results: Twenty-eight patients (38%) relapsed for a median follow-up of 21 months, and there were no differences in baseline clinical characteristics between groups. In the TSAb group, relapse was more common in patients with positive TSAb at ATD withdrawal (67%) than patients with negative TSAb (17%; P=0.007). Relapse-free survival was shorter in TSAb-positive patients. In the TBII group, there were no differences in the relapse rate and relapse-free survivals according to TBII positivity. For predicting Graves disease relapse, the sensitivity and specificity of TSAb were 63% and 83%, respectively, whereas those of TBII were 28% and 65%.

Conclusion: TSAb at ATD withdrawal can predict the relapse of Graves hyperthyroidism, but TBII cannot. Measuring TSAb at ATD withdrawal can assist with clinical decisions making for patients with Graves disease.

Keywords: Graves disease; Hyperthyroidism; Immunoglobulins; Prognosis

INTRODUCTION

Autoantibodies to thyroid-stimulating hormone (TSH, also called thyrotropin) receptor (thyrotropin receptor antibody [TRAb]) have two different main functions; stimulation or blocking of the TSH receptor (TSHR) [1-4]. Graves disease (GD) is an autoimmune disorder that is mediated by the TRAbs that activate TSHR, thereby stimulating thyroid hormone synthe-
TRAbs for Predicting GD Relapse

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ence range, 0.3 to 4 mIU/L; lower detection limit, 0.01 mIU/L) were measured using an immunoradiometric assay (TSH-CTK-3; DiaSorin S.p.A., Saluggia, Italy) with a functional sensitivity of 0.07 mIU/L [28]. The serum fT4 level (normal range, 10.30 to 24.45 pmol/L) was measured using the fT4 radioimmunoassay (RIA) KIT (Immunootech, Prague, Czech Republic). The serum total T3 level (reference range, 1.51 to 2.77 nmol/L) was measured by RIA using T3-CTK (DiaSorin S.p.A.).

**TSAb assays**

For the TSAb assays, the Thyretai TSI reporter Bio Assay (Diagnostic Hybrids Inc., Athens, OH, USA) was used according to the manufacturer’s instructions. The Thyretai kit is a Mc4 assay. The specimen-to-reference ratio (SRR), which is defined as the mean specimen TSI/mean reference TSI, is equal to 100. A specimen was considered positive if SRR was ≥140%.

**TBII assays**

For the TBII assays, the values were detected using the B.R.A.H.M.S. TRAK human RIA (B.R.A.H.M.S. GmbH, Henningsdorf/Berlin, Germany) according to the manufacturer’s recommendation. TBII titers ≥1.5 IU/L were considered positive. The analytical sensitivity was 0.3 IU/L and the functional assay sensitivity was 1.0 ± 0.2 IU/L.

**Statistical analysis**

The statistical analysis was conducted using using SPSS version 21.0 (IBM Co., Armonk, NY, USA). Graphs were produced using Prism version 5.01 (GraphPad Software Inc., La Jolla, CA, USA). The continuous variables are presented as the mean ± SD or medians with IQR. The continuous variables were compared between groups using the Student t test or Mann-Whitney test. The categorical variables are presented as numbers with percentages. The categorical variables were compared between groups using the chi-square test or Fisher exact test. The relapse-free survival (RFS) curves were calculated using the Kaplan-Meier method and the log-rank test was used to compare RFSs according to TRAb titers. The hazard ratio (HR) and 95% confidence interval (CI) used to evaluate the risk of relapse in the TSAb group were derived using Cox proportional hazards modeling. The multivariate analysis included age, sex, presence of a goiter and orbitopathy, thyroid function at baseline, treatment duration of any ATDs, and TSAb. All P values were 2-sided, with $P<0.05$ considered statistically significant.

**RESULTS**

**Baseline characteristics**

The baseline characteristics are listed in Table 1. The mean age of the 74 patients was 31.5 ± 13.2 years, and 56 patients (76%) were female (Table 1). In the median follow-up period of 21.0 months (IQR, 10.0 to 27.5), 28 of 74 patients (38%) demonstrated GD relapse.

In the TSAb group ($n=35$), the mean age was 39.1 ± 14.4 years, and 24 patients (69%) were female (Table 1). Eighteen patients (51%) had a goiter, and six patients (17%) had TAO at the diagnosis of GD. Twenty-eight patients (72%) were treated with MMI, and the median treatment duration using ATDs was 24.0 months (IQR, 18.0 to 32.0). The median duration of euthyroid status while using the minimum dose of ATDs was 10.4 months (IQR, 9.9 to 13.4). Twelve patients (34%) relapsed during the median follow-up period of 15.0 months (IQR, 10.0 to 23.0).

In the TBII group ($n=39$), the mean patient age was 43.6 ± 11.8 years, and 32 patients (82%) were female (Table 1). Twenty-three patients (59%) had a goiter, and four patients (10%) had TAO at the diagnosis of GD. Thirty patients (86%) were treated with MMI, and the median treatment duration with ATDs was 21.0 months (IQR, 16.0 to 26.0). The median dura-

![Fig. 1. Relapse-free survival of Graves disease patients after antithyroid drug withdrawal in the thyroid stimulatory antibody (TSAb) and thyrotropin-binding inhibitory immunoglobulin (TBII) groups. Among 74 patients, there was no significant difference in the relapse-free survival between the TSAb and TBII groups.](image-url)
tion of euthyroid with the minimal maintenance dose of ATDs was 10.6 months (IQR, 9.0 to 14.0). Sixteen patients (41%) relapsed during a median follow-up period of 22.0 months (IQR, 9.0 to 34.0).

There were no significant differences in age, sex, presence of a goiter, ⁹⁹mTc uptake on the thyroid scans, family history of GD, presence of TAO, treatment duration with ATDs, duration of euthyroid status while using a minimal maintenance dose of ATDs, thyroid function at diagnosis (except initial serum TSH levels), TRAbs positivity at withdrawal of ATD, or RFS between the TSAb and TBII groups (Table 1, Fig. 1).

**Clinical characteristics of the patients in the TSAb group according to TSAb at ATD withdrawal**

In the TSAb group (n=35), 23 patients (66%) were negative for TSAb and 12 patients were positive for TSAb at the time of ATD withdrawal. There were no significant differences in age, sex, presence of a goiter, ⁹⁹mTc uptake on the thyroid scans, family history of GD, presence of TAO, treatment duration with ATDs, duration of the euthyroid status using the minimal maintenance dose of ATDs, and thyroid function at diagnosis between the TSAb-positive and -negative patients (Table 2). The fT4 level at ATD withdrawal was higher in TSAb-positive patients (19.3±2.57 pmol/L) than TSAb-negative patients (16.7±2.57 pmol/L, \( P=0.01 \)). There were significantly more cases of relapse in TSAb-positive patients (8 of 12 patients, 67%) than TSAb-negative patients (4 of 23 patients, 17%) during the median follow-up period of 15.0 months (IQR, 10.0 to 23.0; odds ratio, 9.5; 95% CI, 1.9 to 47.7; \( P=0.007 \)) (Table 2).

### Table 1. Baseline Characteristics of the Graves Disease Patients in the TSAb and TBII Groups

| Characteristic                  | Total (n=74) | TSAb group (n=35) | TBII group (n=39) | \( P \) value |
|--------------------------------|-------------|-------------------|-------------------|--------------|
| **Age at diagnosis, yr**       | 31.5±13.2   | 39.1±14.4         | 43.6±11.8         | 0.14         |
| **Female sex**                 | 56 (76)     | 24 (69)           | 32 (82)           | 0.18         |
| **Presence of a goiter**       | 41 (55)     | 18 (51)           | 23 (59)           | 0.51         |
| **Small (<40 g)**              | 24 (32)     | 11 (31)           | 13 (33)           | 0.77         |
| **Medium to large (≥40 g)**    | 17 (23)     | 7 (20)            | 10 (26)           |              |
| **Family history of Graves disease** | 2 (3)   | 1 (3)             | 1 (3)             | 0.99         |
| **Thyroid associated orbitopathy** | 10 (14) | 6 (17)            | 4 (10)            | 0.50         |
| **Antithyroid drug**           |             |                   |                   |              |
| Methimazole                    | 58 (78)     | 28 (72)           | 30 (86)           | 0.16         |
| Carbimazole                    | 9 (12)      | 6 (15)            | 3 (9)             |              |
| Propylthiouracil               | 7 (9)       | 5 (13)            | 2 (6)             |              |
| **Treatment duration of ATD, mo** | 22.0 (16.0–26.5) | 24.0 (18.0–32.0) | 21.0 (16.0–26.0) | 0.19         |
| **Euthyroid duration of ATD, mo** | 10.5 (5.0–17.5) | 10.4 (9.9–13.4) | 10.6 (9.0–14.0) | 0.67         |
| **Thyroid function test at diagnosis** |             |                   |                   |              |
| Total T3, nmol/L               | 4.5±1.9     | 4.3±1.2           | 4.6±2.3           | 0.55         |
| Free T4, pmol/L                | 38.6±16.7   | 38.6±15.4         | 38.6±18.0         | 0.95         |
| TSH, mIU/L                     | 0.05±0.02   | 0.04±0.01         | 0.06±0.03         | 0.02         |
| **Thyroid function test at ATD withdrawal** |             |                   |                   |              |
| Total T3, nmol/L               | 2.2±0.3     | 2.2±0.3           | 2.2±0.3           | 0.92         |
| Free T4, pmol/L                | 16.7±2.6    | 18.0±2.6          | 16.7±2.6          | 0.07         |
| TSH, mIU/L                     | 2.7±3.1     | 2.3±1.9           | 3.2±3.8           | 0.22         |
| Positivity of TSAb or TBII     | 23 (31)     | 12 (34)           | 11 (28)           | 0.87         |
| Follow-up duration, mo         | 21.0 (10.0–27.5) | 15.0 (10.0–23.0) | 22.0 (9.0–34.0) | 0.05         |
| Relapse                        | 28 (38)     | 12 (34)           | 16 (41)           | 0.55         |

Values are expressed as mean±SD, number (%), or median (interquartile range). TSAb, thyroid stimulatory antibody; TBII, thyrotropin-binding inhibitory immunoglobulin; ATD, antithyroid drug; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.
In the TBII group (n=39), 28 patients (72%) were negative for TBII and 11 patients (28%) were positive for TBII at the time of ATD withdrawal. There were no significant differences in age, sex, presence of a goiter, 99mTc uptake on thyroid scans, family history of GD, presence of TAO, treatment duration with ATDs, duration of euthyroid status using the minimal maintenance dose of ATDs, and thyroid function at diagnosis between the TBII-positive and -negative patients (Table 2).

There was no significant difference in the relapse rate between TBII-positive patients (4 of 11 patients, 36%) and -negative patients (12 of 28 patients, 43%) during the median follow-up of 22.0 months (IQR, 9.0 to 34.0) (Table 2).

### Table 2. Clinical Factors in TRAb-Positive and -Negative Patients in the TSAb and TBII Groups

| Variable                              | TSAb (n=35) | TBII (n=39) | P value |
|---------------------------------------|-------------|-------------|---------|
|                                       | Negative (n=23) | Positive (n=12) |          |
|                                       | Positive (n=28) | Positive (n=11) |          |
| **Age at diagnosis, yr**              | 40.3±15.2    | 37.7±13.0   | 0.49    |
| **Female sex**                        | 15 (65)     | 9 (75)      | 0.71    |
| **Presence of a goiter**              | 13 (57)     | 5 (42)      | 0.40    |
| **Small (<40 g)**                     | 10 (43)     | 1 (8)       | 0.05    |
| **Medium to large (≥40 g)**           | 3 (13)      | 4 (33)      | 0.05    |
| **Family history of Graves disease**  | 1 (4)       | 0           | 0.99    |
| **Thyroid-associated orbitopathy**    | 4 (17)      | 2 (17)      | 0.99    |

| **Antithyroid drug**                  |             |             |         |
| **Methimazole**                       | 18 (78)     | 12 (100)    | 0.99    |
| **Carbimazole**                       | 3 (13)      | 0           | 0.11    |
| **Propylthiouracil**                  | 2 (9)       | 0           | 0.42    |

| **Treatment duration of ATD, mo**     | 22.0 (18.0–32.0) | 25.0 (17.0–31.3) | 0.99    |
| **Euthyroid duration of ATD, mo**     | 10.3 (9.9–24.0) | 10.5 (9.8–13.8) | 0.66    |

| **Thyroid function test at diagnosis**|            |             |         |
| **Total T3, nmol/L**                  | 4.3±1.0     | 4.3±1.6     | 0.96    |
| **Free T4, pmol/L**                   | 41.2±16.7   | 36.0±14.2   | 0.55    |
| **TSH, mIU/L**                        | 0.04±0.01   | 0.04±0.004  | 0.42    |

| **Thyroid function test at ATD withdrawal**|            |             |         |
| **Total T3, nmol/L**                   | 2.2±0.3     | 2.3±0.4     | 0.14    |
| **Free T4, pmol/L**                    | 16.7±2.6    | 19.3±2.6    | 0.91    |
| **TSH, mIU/L**                         | 2.4±2.0     | 1.9±1.6     | 0.57    |
| **TSAb or TBII levels**               | 63.9±36.9   | 323.8±146.1 | <0.05   |

| **Follow-up duration, mo**            | 20.0 (11.0–24.0) | 13.0 (5.5–20.3) | 0.14    |
| **Relapse**                           | 4 (17)       | 8 (67)       | 0.01    |

Values are expressed as mean±SD, number (%), or median (interquartile range).

TRAb, thyrotropin receptor antibody; TSAb, thyroid stimulating antibody; TBII, thyrotropin-binding inhibitory immunoglobulin; ATD, antithyroid drug; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

*TSAb titer (%) and TBII (IU/L).

### Clinical characteristics of the patients in the TBII group according to TBII at ATD withdrawal

In the TBII group (n=39), 28 patients (72%) were negative for TBII and 11 patients (28%) were positive for TBII at the time of ATD withdrawal. There were no significant differences in age, sex, presence of a goiter, 99mTc uptake on thyroid scans, family history of GD, presence of TAO, treatment duration with ATDs, duration of euthyroid status using the minimal maintenance dose of ATDs, and thyroid function at diagnosis between the TBII-positive and -negative patients (Table 2).

There was no significant difference in the relapse rate between TBII-positive patients (4 of 11 patients, 36%) and -negative patients (12 of 28 patients, 43%) during the median follow-up of 22.0 months (IQR, 9.0 to 34.0) (Table 2).

### RFS according to TSAb or TBII positivity at ATD withdrawal

In the TSAb group, TSAb-positive patients demonstrated shorter RFS than TSAb-negative patients (P=0.003) (Fig. 2A). When we applied various cut-off values for TSAb positivity at ATD withdrawal, TSAb-positive patients still demonstrated significantly shorter RFS in comparison with TSAb-negative patients (Fig. 2B, C). When we compared TSAb levels at 3 months after ATD withdrawal, the RFS of TSAb-positive patients was also significantly shorter than TSAb-negative patients (Fig. 2D).
In the TBII group, there was no significant difference in RFS between TBII-positive and -negative patients at ATD withdrawal (using three different cut-off values) or at 3 months after withdrawal (Fig. 3).

**Fig. 2.** Relapse-free survival of the patients after antithyroid drug (ATD) withdrawal in the thyroid stimulatory antibody (TSAb) group according to TSAb levels. At ATD withdrawal using a cut-off value of (A) 140%, (B) 130%, (C) 160%, and (D) 3 months after ATD withdrawal.

In the TBII group, there was no significant difference in RFS between TBII-positive and -negative patients at ATD withdrawal (using three different cut-off values) or at 3 months after withdrawal (Fig. 3).

**Diagnostic values of TSAb and TBII for predicting GD relapse**
For predicting GD relapse, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of a positive TSAb value at ATD withdrawal were 63%, 83%, 78%, 69%, and 76%, respectively (Table 3). For a positive TBI, these values were 28%, 65%, 45%, 47%, and 50%, respectively (Table 3).

**Factors associated with GD relapse in the TSAb group**
Patients who had higher TSAb titers at ATD discontinuation
demonstrated more GD relapses ($P=0.002$). Patients with GD relapse demonstrated significantly higher TSAb titers at ATD discontinuation ($P=0.002$) (Fig. 4). The univariate and multivariate analyses were performed to determine the factors associated with relapse in the TSAb group. The TSAb level at ATD withdrawal was the only significant factor associated with relapse on the univariate analysis (HR, 5.21; 95% CI, 1.53 to 17.71; $P=0.008$) (Table 4). On the multivariate analysis, the TSAb level was a significant factor associated with relapse (HR, 6.68; 95% CI, 1.29 to 34.62; $P=0.02$) (Table 4).

**DISCUSSION**

In our current study, TSAb-positive patients demonstrated a higher risk for GD relapse after ATD withdrawal. The TSAb bioassay at ATD withdrawal was more useful for predicting the...
relapse of GD hyperthyroidism in comparison with the TBII assay. This study is the first study demonstrating RFS of the GD patients in the TSAb (Mc4 assay) and TBII (second-generation assay) groups. This study enrolled patients with newly diagnosed GD who were initially treated by dose titrating regimens of ATDs, and they maintained an euthyroid state with a minimum dose of ATDs for \( \geq 6 \) months. All patients were followed using the same protocol after ATD withdrawal. We found statistically significant differences between the TSAb and the TBII assay for predicting the GD hyperthyroidism relapse. The cut-off values for TSAb and TBII at ATD withdrawal were the same as those used for diagnosing of GD.

Measuring TRAbs at the time of ATD withdrawal is useful for predicting GD relapse [3,10,14-24]. GD is characterized by remission and relapse, like many autoimmune diseases. In a meta-analysis conducted 20 years ago, TRAb assays could not demonstrate a sufficient predictive value for GD relapse, mainly due to the low sensitivity and specificity values of earlier assays [6]. However, a recent study reported a significant correlation between serum TRAb levels at the end of MMI treatment and percentage of patients with recurrent hyperthyroidism (\( r=0.56, P<0.001 \)) and time to recurrent hyperthyroidism (\( r=-0.38, P=0.03 \)) [29].

The TBII assay can detect immunoglobulins that inhibit the binding of radio-labeled TSH to TSHRs [25-27,30]. TBII assays that initially used porcine TSHR were shown to have a

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**Table 3. Diagnostic Values of TSAb and TBII at Antithyroid Drug Withdrawal for Hyperthyroidism Relapse in Patients with Graves Disease**

| Variable | TSAb (n=35) | TBII (n=39) |
|----------|-------------|-------------|
|          | Negative (n=23) | Positive (n=12) | Negative (n=28) | Positive (n=11) |
| Relapse | 4 (17) | 8 (67) | 12 (43) | 4 (36) |
| Diagnostic values, % | | | | |
| Sensitivity | 63 | 28 | | |
| Specificity | 83 | 65 | | |
| Negative predictive value | 78 | 45 | | |
| Positive predictive value | 69 | 47 | | |
| Accuracy | 76 | 50 | | |

Values are expressed as number (%).

TSAb, thyroid stimulatory antibody; TBII, thyrotropin-binding inhibitory immunoglobulin.

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**Table 4. Cox Proportional Hazard Modeling for Predicting Graves Disease Relapse in the TSAb Group**

| Variable | Univariate | Multivariate |
|----------|------------|--------------|
|          | HR | 95% CI | \( P \) value | HR | 95% CI | \( P \) value |
| Age at diagnosis, yr | 0.99 | 0.95–1.03 | 0.65 | - | - | NA |
| Male sex | 1.04 | 0.31–3.47 | 0.06 | - | - | NA |
| Goiter (medium to large) | 2.07 | 0.62–6.94 | 0.24 | - | - | NA |
| Thyroid associated orbitopathy | 1.14 | 0.24–5.41 | 0.87 | - | - | NA |
| Severe hyperthyroidism at diagnosis\( ^a \) | 1.63 | 0.20–13.39 | 0.65 | - | - | NA |
| Treatment duration of ATD | 1.00 | 0.99–1.02 | 0.85 | - | - | NA |
| Positive TSAb levels at ATD withdrawal\( ^b \) | 5.21 | 1.53–17.71 | 0.008 | 6.68 | 1.29–34.62 | 0.02 |

TSAb, thyroid stimulatory antibody; HR, hazard ratio; CI, confidence interval; NA, not applicable; ATD, antithyroid drug.

*Severe hyperthyroidism at baseline was defined as serum free thyroxine level >64.4 pmol/L at baseline; *A specimen was considered positive if specimen-to-reference ratio was \( \geq 140\% \).
Tc uptake on thyroid scans are known to predict relapse of GD hyperthyroidism [14]. These findings suggest that the TSAb assay is more useful for predicting relapse in GD patients. A prospective study demonstrated better RFS of the GD patients in the TSAb group (Mc4 assay) than TBII (second-generation assay) groups. Recently, several studies reported the usefulness of the Mc4 assay for predicting relapse in GD patients. A prospective study with over 5 years of follow-up examinations reported that TSAb measurement using the Mc4 assay (Thyretain) can predict hyperthyroidism relapse after ATD withdrawal [22]. The Mc4 assay demonstrated a trend toward improved NPV (82.6% vs. 76.9%) and sensitivity (80.0% vs. 70.0%) in comparison with the M22 assay [22]. One retrospective study reported no significant difference in terms of sensitivity, specificity, PPV, and NPV between the M22 assay and the Mc4-TSAb assay for predicting GD relapse [14]. Using a high Mc4-TSAb cut-off value (230%), a better specificity (85%), and PPV (69%) were shown in comparison with the best cut-off value for the M22 assay [14]. These findings suggest that the TSAb bioassay is useful for predicting the relapse of GD hyperthyroidism. In our current analyses, patients with positive TSAb demonstrated shorter RFS values than patients with negative TSAb ($P=0.003$) (Fig. 2). In contrast, there was no significant difference in RFS between patients with positive and negative TBII titers ($P=0.99$) (Fig. 3). When we applied various cut-off values for TSAb levels, RFS was still significantly shorter in TSAb-positive patients than TSAb-negative patients (Fig. 2).

In addition to the TRAb measurements, many factors such as age, sex, presence of a goiter, family history of GD, thyroid hormone levels, thyroid echogenicity, the results of Doppler US, and $^{99m}$Tc uptake on thyroid scans are known to predict relapse [3,10-13]. However, according to our multivariate analysis, TSAb positivity was the only significant factor associated with relapse (Table 4).

This study has several limitations associated with its retrospective design. First, we enrolled a relatively small number of patients, although these subjects achieved an euthyroid state for ≥6 months with the minimum maintenance dose of ATDs, and all patients were followed using a uniform protocol. Therefore, we were able to compare the relapse rate and RFS during the follow-up period. Second, we did not evaluate the TSAb and TBII levels in the same patients for direct comparison. However, there was no significant difference in the baseline characteristics or RFS between the TSAb and TBII groups. Third, this study was performed in an iodine-sufficient geographical area, and the results cannot be generalized to other populations [33]. Finally, a second-generation TBII assay was used instead of a third-generation M22-based assay. Comparing the M22-based TRAb assay with the second-generation assay, however, they had similar sensitivities and specificities, but the M22-based assay demonstrated significantly lower precision in some ways including a higher intra-assay coefficient of variation [27,34,35].

In conclusion, TSAb assessment at the time of ATD withdrawal could be useful for predicting relapse in ATD-treated GD patients. However, TBII at ATD withdrawal cannot predict GD hyperthyroidism relapse. Measuring TSAb before ATD withdrawal could assist with clinical decision-making for GD patients.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.
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