Early follow-up assessment of thyrotropin receptor antibodies in diverse therapeutic approaches for Graves' Disease

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Abstract

The pattern of change in thyrotropin receptor antibody levels following treatment for Graves' disease(GD) remains elusive. The primary objective of our study is to compare early serum thyrotropin receptor antibody(TRAb) and thyroid-stimulating immunoglobulin(TSI) levels in GD patients receiving antithyroid drug(ATD) therapy versus radioactive iodine(RAI) treatment. We analyzed 162 newly diagnosed GD patients: 123 received methimazole alone (ATD group), while 39 switched to ^{131}I after one month of methimazole due to adverse effects (RAI group). TRAb and TSI levels were measured at baseline and multiple follow-up timepoints specific to each treatment protocol. The ATD group showed stable TRAb/TSI levels at 1-3 months, with significant declines from 6 months onward. In contrast, the RAI group demonstrated sharp increases in both antibodies at 1 month post-^{131}I, with levels remaining substantially elevated before beginning to decline at 10 months. At the 1-month post-treatment timepoint, both TRAb and TSI levels were significantly lower in the ATD group compared to the RAI group. Furthermore, the changes in serum TRAb/TSI levels following medication in the RAI group were independent of the administered dose. Antibody positivity rates decreased progressively in the ATD group but persisted >90% in the RAI group throughout follow-up. Methimazole monotherapy achieves gradual TRAb/TSI reduction from 6 months onward, while ^{131}I therapy triggers rapid antibody elevation within 1 month followed by slow decline. These findings highlight distinct antibody dynamics between treatment modalities, supporting differential monitoring strategies during follow-up.

Full Text

Preamble

Early Follow-up Assessment of Thyrotropin Receptor Antibodies in Diverse Therapeutic Approaches for Graves' Disease

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Abstract

The pattern of change in thyrotropin receptor antibody levels following treatment for Graves' disease (GD) remains elusive. The primary objective of our study is to compare early serum thyrotropin receptor antibody (TRAb) and thyroid-stimulating immunoglobulin (TSI) levels in GD patients receiving antithyroid drug (ATD) therapy versus radioactive iodine (RAI) treatment. We analyzed 162 newly diagnosed GD patients: 123 received methimazole alone (ATD group), while 39 switched to ^{131}I after one month of methimazole due to adverse effects (RAI group). TRAb and TSI levels were measured at baseline and at multiple follow-up time points specific to each treatment protocol. The ATD group showed stable TRAb/TSI levels at 1–3 months, with significant declines from 6 months onward. In contrast, the RAI group demonstrated sharp increases in both antibodies at 1 month post-^{131}I, with levels remaining substantially elevated before beginning to decline at 10 months. At the 1-month post-treatment time point, both TRAb and TSI levels were significantly lower in the ATD group compared to the RAI group. Furthermore, the changes in serum TRAb/TSI levels following medication in the RAI group were independent of the administered dose. Antibody positivity rates decreased progressively in the ATD group but persisted >90% in the RAI group throughout follow-up. Methimazole monotherapy achieves gradual TRAb/TSI reduction from 6 months onward, whereas ^{131}I therapy triggers rapid elevation of antibodies within 1 month, followed by a slow decline. These findings highlight distinct antibody dynamics between treatment modalities, supporting differential monitoring strategies during follow-up.

Keywords: Graves' disease, TRAb, TSI, Early follow-up

I. Introduction

Graves' disease (GD) is a systemic autoimmune disorder characterized by the infiltration of thyroid antigen-specific T and B lymphocytes into tissues expressing the thyrotropin receptor (TSHR) [**?**]. It is the most common cause of hyperthyroidism, with a global incidence of approximately 0.5% in men and 2% in women [**?**]. The pathogenesis remains unclear but is believed to involve the activation of autoreactive B cells by autoreactive T cells under the influence of genetic and environmental factors, leading to the production of TSHR antibodies (TRAb) [**?**]. These antibodies bind to TSHR on thyroid follicular cells, resulting in hyperthyroidism. TSHR antibodies exist in three primary forms: thyroid-stimulating immunoglobulin (TSI), thyrotropin-binding inhibitory immunoglobulins (TBII), and neutral TRAb, which bind to different sites on TSHR and exert distinct biological effects [**?**]. The TSI assay, utilizing automated bridge technology, was specifically designed to detect TSI [**?**] and has shown significant clinical utility, exhibiting exceptional sensitivity and specificity for diagnosing GD [**?**]. However, the advantages of TSI in monitoring treatment efficacy and predicting prognosis in GD remain unclear.

Substantial evidence from the literature confirms that both assays exhibit good repeatability and within-laboratory precision [**?**]. Both TRAb and TSI assays demonstrate high sensitivity and specificity for Graves' disease; however, direct comparison and interchangeability between these two assays are not feasible [**?**]. This discrepancy can be primarily attributed to methodological differences. The TSI assay, which utilizes a chimeric bridging interaction construct, is designed primarily to measure the stimulatory form of TRAb, whereas the TRAb assay measures the total pool of antibodies present in the serum, including both TSI and TBII. Furthermore, fundamental differences exist in calibration systems: TSI is calibrated against the 2nd International Standard for Thyroid Stimulating Antibody, which is based on stimulating monoclonal antibodies of defined concentration and specificity, while TRAb is calibrated using the 1st International Standard, which comprises a mixture of stimulating and inhibiting immunoglobulins extracted from the human plasma of a pregnant woman [**?**]. This study also aimed to compare longitudinal changes in TRAb and TSI levels during follow-up after different treatment modalities for GD.

The diagnosis of GD primarily relies on clinical manifestations, physical examination, serum biochemical markers (thyroid hormones and TSH), imaging studies, and immunological markers such as TRAb. TRAb is a crucial biomarker for accurate diagnosis, differential diagnosis, and determination of the timing of discontinuation of antithyroid drug (ATD) therapy in GD [**?**]. The main treatment options for GD include ATD, radioactive iodine therapy (RAI), and thyroidectomy (TX) [**?**, **?**]. The long-term clinical outcomes of the two most widely used treatments, ATD and RAI, remain unclear. Current evidence indicates that pretherapeutic TRAb and TSI levels are associated with the prognosis of GD [**?**]; however, comparative analysis of the dynamic changes in antibody levels during the course of different treatment modalities remains limited. This study

aimed to compare the early follow-up results of TRAb and TSI in patients with GD treated with ATD and RAI to elucidate their clinical characteristics.

II. Materials and Methods

II.1 Patients

This retrospective study included patients diagnosed with GD at the Department of Nuclear Medicine and Endocrinology, Shanghai General Hospital, between 2022 and 2023. GD diagnosis was based on clinical symptoms of hypermetabolism (e.g., palpitations, tremors, and sweating), thyroid enlargement, elevated serum thyroid hormones, decreased TSH, elevated TRAb and TSI levels, and ultrasound findings of diffuse thyroid enlargement. Patients under 18 years of age, pregnant women, and those with hyperthyroidism complicated by tumors were excluded. A total of 162 newly diagnosed GD patients who achieved remission (normalization of serum thyroid hormones and TSH and discontinuation or maintenance of minimal ATD dosage) were included.

Among them, 123 patients were treated with methimazole alone (ATD group), whereas 39 patients underwent ^{131}I therapy after one month of methimazole treatment because of adverse effects (25 cases of liver injury, 9 cases of leukopenia, and 5 cases of allergy) (RAI group). For the initial treatment, patients received methimazole (MMI, 15–30 mg/day). Doses were titrated according to standard protocols, and a subset of patients was maintained on a low-dose regimen (MMI 2.5 mg/day) after normalization of thyroid function. Patients scheduled for RAI therapy were placed on a low iodine diet. Antithyroid drugs were discontinued for at least seven days before thyroid scintigraphy. Thyroid volume was assessed by 24-hour ^{131}I uptake and ^{99} Tc-pertechnetate scintigraphy and calculated using the ellipsoid formula. The administered activity of radioiodine was determined to deliver an absorbed dose of 300 Gy to the thyroid gland in patients with Graves' disease, calculated using the Medical Internal Radiation Dose (MIRD) methodology per institutional protocol.

II.2 Laboratory Measurements

Serum TSH levels were measured using chemiluminescence assays (Autobio6200 analyzer; Zhengzhou Autobio Diagnostics). Serum FT3 and FT4 levels were determined using radioimmunoassay kits (Medipan, Germany) according to the manufacturer' s instructions. Reference ranges were 0.35–4.75 μIU/mL for TSH, 3.8–8.5 pmol/L for FT3, and 10.2–22.5 pmol/L for FT4. TRAb levels were measured using an electrochemiluminescence immunoassay (Cobas e801 analyzer; Roche Diagnostics, Switzerland), with a positive cutoff of $ $1.75 IU/L. TSI levels were measured using a chemiluminescence immunoassay (IMMULITE 2000 analyzer, Siemens, USA), with a positive cutoff of $ $0.55 IU/L.

II.3 Statistical Analysis

Categorical variables are presented as numbers (percentages). Normally distributed continuous variables are described as the mean ± standard deviation, while non-normally distributed continuous variables are described as the median (interquartile range, IQR P25–P75). The Student' s t-test or Mann–Whitney U test was used to compare the clinical characteristics between the groups. Chi-square tests were used to compare the rates. All statistical analyses were performed using SPSS Statistics (version 18.0; IBM Corp., USA) and graphs were generated using GraphPad Prism 5.0 (GraphPad Software, USA). Statistical significance was set at $P < 0.05$.

III. Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Shanghai General Hospital (Approval No. 2025KS377). The requirement for informed consent was waived according to the hospital policy for retrospective studies.

IV. Results

IV.1 Baseline Characteristics of the Patients

The baseline characteristics of the ATD and RAI therapy groups (sequential MMI-to-RAI therapy) are shown in Table 1 . No significant differences were observed in terms of age or sex between the two groups. At baseline, the RAI therapy group had significantly higher serum FT3, FT4, and TT3 levels than the ATD group, whereas TT4, TRAb, and TSI levels showed no significant differences.

Table 1. Baseline Characteristics of the ATD and RAI Groups

Variable	ATD Group (n=123)	RAI Group (n=39)	P-value
Age (years)	41.1 ± 13.1	40.0 ± 9.64	-
Gender, Male	38/123 (30.9%)	11/39 (28.2%)	-
FT3 (pmol/L)	16.87 (10.74, 26.35)	23.21 (16.69, 29.03)	0.0007*
FT4 (pmol/L)	42.17 (28.03, 54.01)	51.32 (45.28, 61.81)	0.0004*
TT3 (nmol/L)	4.69 (3.47, 6.79)	4.92 (4.24, 7.32)	0.0181*
TT4 (nmol/L)	241.4 (176.5, 288.6)	262.4 (210.4, 321.3)	-
TRAb (IU/L)	9.04 (3.61, 17.2)	10.60 (4.92, 21.13)	-
TSI (IU/L)	5.52 (2.52, 13.2)	8.09 (3.01, 17.08)	-

FT3, Free Triiodothyronine; FT4, Free Thyroxine; TT3, Total Triiodothyronine;

TT4, Total Thyroxine; TRAb, thyrotropin receptor autoantibody; TSI, thyroid-stimulating immunoglobulin. Statistically significant ($P < 0.05$).*

IV.2 Follow-up Results

The follow-up results of TRAb and TSI levels within one year of treatment are shown in Figure 1 [Figure 1: see original paper]. In the ATD group, TRAb levels at 1 and 3 months post-treatment showed no significant difference compared to baseline but significantly decreased at 6 and 12 months. TSI levels followed a similar trend. In the RAI group, TRAb levels significantly increased at 1 month post-^{131}I therapy compared to baseline and decreased at 10 months compared to 4 months (Fig. 1a, c). TSI levels exhibited a similar pattern (Fig. 1b, d). TRAb and TSI levels 1 month post-treatment were significantly lower in the ATD group than in the RAI therapy group (Fig. 1e).

Figure 1. Boxplots of TRAb and TSI levels in the ATD and RAI groups within one year of treatment. TRAb, thyrotropin receptor autoantibody; TSI, thyroid-stimulating immunoglobulin; ATD, antithyroid drug; RAI, radioactive iodine. *: The follow-up results showed a statistically significant difference compared with the previous assessment.

IV.3 The Association Between Follow-up Levels of TRAb and TSI and the Therapeutic Dosage in the RAI Group

To determine whether post-RAI changes in TRAb and TSI levels were dose-dependent, we conducted a further analysis of the RAI group' s characteristics. The statistical results are summarized in Table 2 . We divided the patients into a high-dose group ($ $10 mCi) and a low-dose group (<10 mCi) based on the treatment dose and statistically analyzed the characteristics of the two groups. A significant disparity in thyroid volume was observed between the treatment groups. Pre-treatment assessments of 24-hour radioactive iodine uptake and TRAb/TSI levels showed no intergroup difference, indicating that the alterations in TRAb/TSI following RAI therapy are not discernibly influenced by the treatment dose.

Table 2. The Demographic and Clinical Characteristics of the Patients in the RAI Group

Variable	low-dose group (<10 mCi)(n=22)	high-dose group ($ $10 mCi)(n=17)	P-value
Age (years)	40.9 ± 9.9	38.8 ± 9.7	-
Gender, Male	5/22 (22.7%)	6/17 (35.3%)	-
Goitre size	14/22 (63.6%)	4/17 (23.5%)	0.013*

Variable	low-dose group (<10 mCi)(n=22)	high-dose group ($ $10 mCi)(n=17)	P-value
24-hour Radioactive Iodine Uptake (%)	69.2 ± 15.9	75.9 ± 16.4	-
At RAI treatment			
TRAb (IU/L)	16.8 (7.2, 30.2)	10.7 (4.2, 26.6)	-
TSI (IU/L)	26.9 (11.48, 39.1)	24.3 (13.5, 40.0)	-
At 1 month following RAI treatment			
TRAb (IU/L)	35.5 (22.4, 39.9)	34.1 (16.2, 40.0)	-
TSI (IU/L)	39.9 (22.4, 40.0)	40.0 (18.0, 40.0)	-
At 4 months following RAI treatment			
TRAb (IU/L)	38.9 (24.4, 40.0)	39.9 (25.8, 40.0)	-
TSI (IU/L)	40.0 (24.2, 40.0)	40.0 (24.5, 40.0)	-
At 10 months following RAI treatment			

Variable	low-dose group (<10 mCi)(n=22)	high-dose group ($ $10 mCi)(n=17)	P-value
TRAb (IU/L)	21.7 (9.5, 25.5)	12.0 (7.9, 21.6)	-
TSI (IU/L)	38.7 (19.0, 40.0)	32.3 (21.8, 40.0)	-

RAI, Radioactive Iodine. The difference between the two groups was statistically significant ($P < 0.05$).*

IV.4 Follow-up Results of TRAb and TSI Positivity Rates

The positive rates of TRAb and TSI within one year of treatment are shown in Figure 2 [Figure 2: see original paper]. Pearson' s correlation analysis revealed a strong linear relationship between TRAb and TSI levels in untreated patients (Pearson correlation coefficient r=0.68) (Fig. 2a). In the ATD group, the positivity rates of TRAb and TSI gradually decreased over one year, with TRAb declining more significantly than TSI at 6 and 12 months (Fig. 2b). In contrast, the positivity rates in the RAI therapy group remained above 90% after one year (Fig. 2c).

Figure 2 [Figure 2: see original paper]. Positive rates of TRAb and TSI in the ATD and RAI therapy groups within one year of treatment. TRAb, thyrotropin receptor autoantibody; TSI, thyroid-stimulating immunoglobulin; ATD, antithyroid drug; Sequential therapy, 39 patients underwent ^{131}I therapy after one month of methimazole treatment because of adverse effects (25 cases of liver injury, 9 cases of leukopenia, and 5 cases of allergy). *: There was a significant difference in the positivity rates of TRAb and TSI.

V. Discussion

As the most common cause of hyperthyroidism, GD is a systemic disease characterized by excessive thyroid hormone production due to autoantibodies that target TSHR. ATD, RAI, and thyroidectomy are the three main treatment options for GD [**?**, **?**]. Antithyroid drugs, including methimazole (MMI), carbimazole (converted to MMI), and propylthiouracil (PTU), inhibit thyroid hormone synthesis and secretion. MMI is the first-line treatment for non-pregnant patients [**?**]. Adverse effects of ATD include allergies, leukopenia, and liver injury [**?**]. Studies have reported that 30%–50% of patients achieve remission (normal TSH and negative TRAb) after 12–18 months of ATD treatment, with a high risk of relapse within 6 months of discontinuation, particularly in patients with persistent TRAb positivity [**?**, **?**].

Thyroidectomy is indicated in patients with suspicious or malignant thyroid nodules, compressive symptoms, or moderate-to-severe Graves' ophthalmopathy. It provides a rapid cure but requires lifelong thyroid hormone replacement [**?**]. RAI is a curative treatment for GD that aims to induce hypothyroidism. Thyroid function should be monitored every 4–6 weeks for 6 months post-RAI or until hypothyroidism is stabilized with hormone replacement [**?**]. Repeat treatment is recommended if hyperthyroidism persists after 6 months [**?**]. RAI may exacerbate Graves' ophthalmopathy, particularly in smokers or patients with high TRAb titers [**?**, **?**]. In China, many patients prefer ATD owing to concerns about radiation and treatment convenience, opting for RAI only when ATD is ineffective or causes adverse effects. Early efficacy evaluation, treatment characteristics, and long-term outcomes of ATD and RAI remain unclear [**?**]. This study aimed to explore the early clinical features of TRAb and TSI in patients with GD treated with ATD and RAI to understand the immunological progression of GD.

The baseline characteristics of the ATD and RAI therapy groups showed no significant differences in terms of age or sex. However, the RAI therapy group had significantly higher baseline FT3, FT4, and TT3 levels, suggesting a potential correlation between baseline thyroid hormone levels and ATD treatment efficacy or adverse effects. Patients in this region predominantly selected ATD as the first-line therapy, influenced by its accessibility and prevailing concerns about radiation exposure from RAI. The transition to RAI typically occurs following suboptimal responses or adverse drug reactions to ATD. Our data indicate that elevated serum thyroid hormone levels at diagnosis may predict both inadequate efficacy and increased susceptibility to adverse events associated with ATD. The comparable TRAb and TSI levels between the groups ensured that these parameters did not confound subsequent treatment outcome assessments. Further research is required to confirm these findings.

This study demonstrated that GD patients treated with ATD exhibited a gradual decline in TRAb and TSI levels, with significant reductions starting at six months. In contrast, RAI-treated patients showed a rapid increase in TRAb and TSI levels within 1 month, likely due to thyroid tissue destruction and antigen exposure [**?**], followed by a decline after 10 months. Evidence from previous studies indicates that although RAI induces varying autoantibody profiles [**?**], longitudinal assessments did not correlate with treatment efficacy after one year [**?**]. Rather, these assessments showed sustained high antibody concentrations, which is consistent with the results of our study. This study demonstrated that TRAb and TSI levels began to decline 10 months post-RAI therapy, which is notably earlier than the 12-month timeframe reported in other studies. This discrepancy might be attributable to the fact that our cohort consisted of newly diagnosed patients who had undergone one month of ATD treatment prior to RAI [**?**]. The serum levels of TRAb and TSI remained persistently high within 10 months of RAI treatment, suggesting that immunological markers are not suitable for assessing therapeutic efficacy or predicting prognosis. Additionally, it is recommended that patients abstain from pregnancy and breastfeeding for

a minimum of six months following RAI therapy, and attempts to conceive should be postponed for 10 months. Investigating the follow-up significance of serum immunological markers in RAI therapy requires more extended and larger cohort studies.

This study stratified the RAI treatment cohort into high- and low-dose subgroups using a 10 mCi therapeutic dosage as the cutoff. A comparative analysis was performed between these subgroups for demographic and clinical parameters, including age, gender, goiter size, 24-hour radioactive iodine uptake (RAIU), and levels of TRAb and TSI at predefined pre- and post-treatment intervals. The findings demonstrated a lack of statistically significant differences in all evaluated metrics, with the sole exception of thyroid volume. This observation is attributable to the fact that the therapeutic dosage was intrinsically determined by thyroid gland size. Irrespective of the administered radioactivity, the cytodestructive action of RAI on thyroid follicular cells facilitates the release of TSHR antigens into the systemic circulation [**?**]. This antigenic exposure precipitates a systemic immune response, culminating in a pronounced surge in autoantibody production within one month post-treatment. Notably, the majority of antibody titers in both cohorts reached the upper quantitation limit of the standard assay [**?**]. Therefore, whether a dilution-based assay would reveal a statistically significant disparity in antibody titers between the high- and low-dose subgroups remains an open question, necessitating further systematic investigation.

Evidence suggests that while TRAb/TSI levels at diagnosis are prognostic of ATD outcomes [**?**, **?**], levels at ATD cessation correlate with RAI success [**?**, **?**]. Data from our ongoing follow-up study will provide further insight into these correlations. A strong linear correlation was observed between TRAb and TSI levels in untreated patients. Multiple studies have indicated that both possess high sensitivity and specificity for the diagnosis and differential diagnosis of GD, underscoring their importance as key immunological indicators [**?**]. Within one year of treatment, TRAb and TSI levels showed no significant differences, except for a lower TRAb positive rate at 6 months in the ATD group, possibly due to methodological differences in their detection. It is also possible that this observation is linked to changes in the autoantibody profiles occurring throughout the treatment process. In the present study, the follow-up trends of TSI and TRAb were comparable across the two treatment strategies [**?**, **?**]. Considering the cost-effectiveness, tracking either marker would be adequate for follow-up purposes.

This study had several inherent limitations. Its retrospective design and relatively small sample size may have introduced unavoidable bias. Consequently, our conclusions warrant verification through more rigorous, prospective studies.

In conclusion, this study elucidated the early changes in serum TRAb and TSI levels in patients with GD treated with ATD and RAI therapy, providing clinical evidence for understanding the immunological progression of GD. The distinct dynamics of TRAb and TSI levels (a gradual decrease with ATD versus an initial

increase followed by a decrease with RAI) must be recognized by clinicians for proper interpretation of tests in the early treatment period.

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Conflict of Interest

These authors declare that they have no competing interests.

Author Contributions

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Note: Figure translations are in progress. See original paper for figures.