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Measuring TSH receptor antibodies: Indications and Clinical Use

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Introduction

TSH receptor antibodies (TRAb), key pathogenetic molecules in Graves' disease (GD), can be detected by second and third generation diagnostic assays with a sensitivity and specificity of over 95%. A recent paper (1) examines the role of these antibodies in clinical practice.

Serum level of TRAb and choice of treatment

In a prospective randomized trial of 131 patients followed up for 5 years, serum TRAb level gradually declined, and after 18 months disappeared in about 70% of patients treated with anti-thyroid drugs (ATD) (n = 48) and surgery (n = 47). In the group treated with radioactive iodine (RAI) (n = 36) the serum level gradually increased for up to 12 months, with gradual reduction thereafter. The patients who relapsed after discontinuation of ATD had TRAb levels which remained positive despite 18 months of ATD and increased further at recurrence, while still below baseline value. Initial TRAb values and their fall during therapy overlapped between patients who remained euthyroid and those who relapsed.

Serum level of TRAb and ability to predict relapse

Incidence of relapse after suspension of ATD is about 50-70%. It would be important to be able to predict *ab initio* the patients at highest risk of relapse. A meta-analysis of studies based on first generation assays from 1975 to 1991 showed a positive predictive value (PPV) too low for clinical use. However, studies employing assays of second and third generation, with at least a year of follow-up following cessation of ATD, show that:

- A serum level ≥12 IU/L at diagnosis is associated with 60% risk of relapse at 2 years and 84% at 4 years.
- A serum level ≥7.5 IU/L at 12 months or ≥3.85 IU/L at cessation of ATD at 18 months is associated with over 90% risk of relapse at 4 years.

In this study, GD also recurred in about 20% of patients with TRAb serum level <3.85 IU/L, but the relapse in this group was much delayed in comparison to those with TRAb serum level above the cut-off (median time to relapse 56 vs. 8 weeks). TRAb measurement 4 weeks after stopping ATD also showed good PPV for risk of relapse.
Attempts at creating prediction models which adjusted for age, goiter size, serum FT4, TRAb and DNA analysis have a restricted role in clinical practice due to cost and limited availability of genetic testing.
The predictive values of TRAb assays based on the thresholds discussed above are summarized in table.

Timing	Serum Threshold	PPV relapse	NPV relapse
Diagnosis	>12 IU/L	60% at 2 years, 84% at 4 years	60% at 2 years, 36% at 4 years
12th months of ATD	>7.5 IU/L	97%	44%
18th month of ATD	>3.85 IU/L	97% at 4 years	79% at 4 years

The risk of relapse seems particularly high if the TSH remains suppressed during treatment with methimazole >5 mg/day. TRAb testing, due to its high specificity and low sensitivity in predicting relapse, is a «rule in» test, useful to select the patients to envoy to RAI or surgery.

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The authors have also analyzed, based on a British and Australian setting, the cost of three different management models, taking into account quality-adjusted life years, efficacy, incidence of relapse and treatment-related complications. At £141 ($182, €160), the TRAb-based model followed by ablative therapy is significantly less expensive than protracted ATD at £16,866 ($21,778, €19,221), even when the cost of treatment with RAI at £5425 ($6,988, €6,128) or surgery at £7,115 (€8,108, $9,188) is factored in.

Serum level of TRAb in pregnancy (1,2)

Use

- Differential diagnosis of GD vs. gestational thyrotoxicosis in women with *hyperemesis gravidarum* and clinical signs of thyrotoxicosis.
- Determination of the risk of thyrotoxicosis in the fetus and in the newborn.

Serum level of TRAb drops in pregnancy, particularly after the 20th week. In a study of 47 pregnant women, a cut-off of 5 UI/L in the second trimester (about 3 times above the upper normal limit) showed sensitivity 100% and specificity 43% in predicting neonatal hyperthyroidism.

Indications (2)

- GD on ATD.
- Previous thyroidectomy or RAI for GD.
- Previous conception of a baby with hyperthyroidism.

Timing (2)

- Early pregnancy.
- Between the 8th and 22nd week if level rose on previous testing.
- Between the 30th and 34th week if level rose on previous testing.

Serum concentration of TRAb and Thyroid Eye Disease (TED)

Raised TRAb levels at diagnosis and during follow-up are associated with the most severe form of TED. Dosing TRAb may assist in selecting steroid prophylaxis in patients undergoing treatment with RAI, in order to prevent appearance or progression of TED. In a prospective study of 159 patients, a cut-off of 8.8 IU/L after 5-8 months from the onset of TED increased the risk of severe ophtalmopathy 18 times.

Comment

Properly used, TRAb can facilitate current clinical practice. While cut-offs adjusted for the different clinical scenarios represent an improvement over a dichotomic (positive vs. negative) approach, no mathematical model can rigidly dictate therapeutic choices. A comprehensive clinical evaluation, which also accounts for patient's adherence to proposed therapy, remains essential.

References

1. Hesarghatta Shyamasunder A, Abraham P. Measuring TSH receptor antibody to influence treatment choices in Graves' disease. Clin Endocrinol 2017, 86: 652–7.
2. Ross DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016, 26: 1343–421.