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# Clinical THYROIDOLOGY

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## Newer TSH Receptor Antibody Assays May Sometimes Be a Useful Additional Factor for Predicting which Graves' Patients Will Remain in Remission when Antithyroid Drugs are Stopped

Giuliani C, Cerrone D, Harii N, Thornton M, Kohn LD, Dagia NM, Bucci I, Carpentieri M, Di Nenno B, Di Blasio A, Vitti P, Monaco F, Napolitano G. A TSHR-LH/CGR chimera that measures functional thyroid-stimulating autoantibodies (TSAb) can predict remission or recurrence in Graves' patients undergoing antithyroid drug (ATD) treatment. *J Clin Endocrinol Metab.* April 6 2012 [Epub ahead of print]. doi: 10.1210/jc.2011-2897.

### SUMMARY

#### Background

Many factors are reportedly associated with the likelihood that Graves' disease will relapse after antithyroid drug treatment is discontinued, but most do not occur with the consistency needed to be very useful clinically. The current paper assessed the ability of several different assays of TSHR antibody levels to predict remission or relapse. Two cell lines (HEK293 and the commercial Thyretain CHO) used "Mc4," a modified human TSHR DNA sequence with a part of its extracellular domain replaced by the similar domain present in the rat LHR. Changing this sequence eliminated a region that was thought to bind some TSHR-blocking antibodies. Predictions based on assays using these two cell lines were compared with predictions based on a commercial ELISA that detects both stimulating and blocking antibodies that compete with the anti-TSHR monoclonal M22. Four authors of the article indicated competing interests concerning the Mc4 assays.

#### Methods

Serum samples were obtained from 40 female and 15 male patients with Graves' disease, before and after antithyroid drugs were given for 12 to 48 months at the Chieta University Endocrinology Clinic. Serum obtained at the initial diagnosis was assayed using HEK239 cells that expressed Mc4 plus one of three different cAMP response element-luciferase reporters, and all patients needed to have an above-normal TSHR antibody level based on this assay. All patients had symptoms of hyperthyroidism, a diffuse goiter or ophthalmopathy, a high serum FT<sub>4</sub>, an undetectable TSH, an enlarged thyroid on ultrasound with a hypoechoic image, or increased uptake on a radioiodine scan. Of the 55 patients, 28 had

*continued on next page*

[Back to Contents](#)

# Newer TSH Receptor Antibody Assays May Sometimes Be a Useful Additional Factor for Predicting which Graves' Patients Will Remain in Remission when Antithyroid Drugs are Stopped

Giuliani C, et al.

remained in remission for 12 to 168 months after the drugs had been withdrawn, 12 had relapsed 2 to 36 months after the drugs had been withdrawn, and 15 remained on antithyroid drugs because of evidence of persistent disease.

Serum samples on 42 patients were available for two additional assays: CHO cells expressing Mc4 plus a cAMP reporter (Thyretain, Diagnostic Hybrids, Athens, OH) and biotin-labeled monoclonal M22 that binds to unoccupied sites on hTSHR coated on ELISA plates (RSR Ltd., Pentwyn, Cardiff, United Kingdom). Assay variability was reduced by averaging three assays of duplicates of each sample. (Note that neither of these commercial assays were the automated versions reviewed in the January 2012 issue of *Clinical Thyroidology*.)

## Results

The mean TSHR antibody level (based on the HEK Mc4 assay) was significantly lower in the group of patients who remained in remission as compared with the combined results of those who relapsed plus those in whom drug treatment was continued. The antibody levels present in most of the individuals who remained in remission had fallen into the normal range on all three assays at the time the drugs

were discontinued (22 of 28 on the HEK Mc4 assay, 16 of 22 on the Thyretain CHO cells, and 19 of 22 on the M22 ELISA). However, this also means that when drugs were discontinued, the levels were still high in a substantial minority of patients who nonetheless did remain in remission (in 6, 6, and 3 patients, respectively). On the other hand, only a few of the patients who relapsed had normal antibody levels (2 of 12, 2 of 8, and 2 of 8, respectively). Most of the patients who had persistent disease and suppressed TSH levels maintained high antibody levels (15 of 15, 11 of 12, and 9 of 12, respectively). Thyroid volume at the end of treatment was significantly less in those who remained in remission: about  $15 \pm 7$  ml versus  $25 \pm 13$  ml in those who relapsed and versus  $30 \pm 10$  ml in those who remained on therapy.

## Conclusions

All three assays seemed have some utility in predicting remission or relapse in patients with Graves' disease; based on the relatively small number of patients available, no major differences were apparent. A larger prospective study on all patients with hyperthyroidism (not preselected for a positive Mc4 assay) might provide more definitive results and could provide a deeper insight into possible mechanisms of immunoglobulin actions on the TSHR.

## ANALYSIS AND COMMENTARY ● ● ● ● ●

If a patient with Graves' disease has taken antithyroid drugs for a year or more, the thyroid has shrunk to or below normal size, and the TSHR antibody level (measured with one of the newer assays) has normalized, then the odds favor a durable remission. However, even when the authors tried to adjust the cutoff values on the tests, the predictions sometimes were wrong. Other factors beyond thyroid size and the levels of TSH and TSHR antibodies are also important in determining whether or not a case will remain in remission. The TSHR is not simply a spigot that regulates the level of cAMP production. The intensity and duration of stimulation by TSH and/or various

antibodies can affect posttranslational modifications, multimer formation, internalization, and associations with other cellular proteins (1, 2). Moreover, even if there were an assay that could measure all stimulating, blocking, and neutral antibodies separately, relapse rates would still be affected by differences in patients with regard to the development of self-tolerance, the thyroid's responsiveness to TSH and anti-TSHR antibodies, and the body's many responses to changing levels of thyroid hormone, as well as in the degree of autoimmune damage to the thyroid and the ability to repair that damage.

— Stephen W. Spaulding, MD  
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
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Giuliani C, et al.


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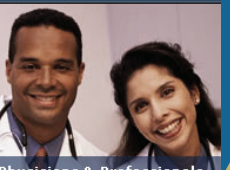
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