

Could Measuring Single-Nucleotide Polymorphisms (SNPs) Become Useful for Predicting a Relapse of Graves' Disease After Antithyroid Drugs Are Discontinued?

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SUMMARY ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ●

Background

When antithyroid drug treatment is discontinued, Graves' disease commonly recurs. The risk of relapse may be increased if a patient still has a goiter, has a persistently positive TSH receptor (TSH-R) antibody, and/or is an active smoker. Cytotoxic T-lymphocyte antigen 4 (CTLA4) is a highly polymorphic gene implicated in many autoimmune disorders. Several of its many single-nucleotide polymorphisms (SNPs) have been associated with increased risk for Graves' disease. The authors of the current paper have previously published data on some very similar patients, which indicate that having G/G alleles at rs231775 in CTLA4 is associated with an increased risk of relapse after antithyroid drugs are discontinued. They now have addressed SNPs in some other autoimmune-related genes as well, plus clinical and lab factors thought to have predictive value, to see whether they improved the accuracy of predicting relapse.

Methods

From 2001 to 2007, a total of 262 patients with Graves' disease were treated with antithyroid drugs alone. At diagnosis, all had a high serum T₄ and/or T₃ plus a suppressed TSH, diffuse uptake of 99mTcO₄ or ¹³¹I, and either a positive TBII assay ("TR-AB" CISbio, which measures whether a patient's IgG will block the binding of 125I-labeled porcine TSH to solubilized porcine TSH receptors bound on plastic tubes) or positive antimicrosomal antibodies. The initial

daily dose of MMI (140 patients, generally given 30 mg) or PTU (79 patients, generally given 300 mg) was reduced as serum T_4 and T_3 normalized, generally reaching a low maintenance dose by 4 months. An additional group of 43 patients was given "block-and-replace" treatment with MMI (5 to 10 mg) plus 50 μ g of L- T_4 to maintain euthyroidism. Patients who became euthyroid smoothly usually stopped antithyroid drugs by 12 months. (An unknown number whose antithyroid drug dose could not be reduced or who had persistently large goiters received antithyroid drugs for 2 to 3 years). After drugs were stopped, patients were followed every 3 months for the first year and every 6 months thereafter. The patients were divided into three groups. Those who had a relapse within 9 months, deemed "early relapses," had been treated for a mean of 30 months. Those who had a relapse between 10 and 36 months, deemed "late relapses," had been treated for a mean of 21 months. Those who had not had a relapse, deemed "long-term remissions," also had been treated for a mean of 21 months (some subsequently did have a relapse). At the end of follow-up, SNPs (three in CTLA-4, eight in CD28, six in ICOS and six in CD40) were assessed; current smoking (38 of 39 smokers were men), goiter size, serum T_4 , T_3 , and TBII levels, antithyroid regimen, and duration were also analyzed. Continuous data were analyzed by one-way ANOVA, categorical data by chi-square or Fisher's exact test, and the strength of associations by Cox proportional-hazards analysis; the P value was adjusted for multiple comparisons.

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Results

Only four SNPs were significantly associated with an increased risk of relapse at both 9 and 36 months (G/G in CTLA-4, plus three SNPs in CD40). Adding up the number of the risk alleles improved the prediction of relapse, although the combined risk alleles didn't reach the adjusted odds ratio of 2.2 or 3.1 the authors reported when using only G/G at rs231775 in their previous studies. Multivariate analysis showed that the hazard ratio (HR) for relapse was increased by a persistently high TRAb at the end of treatment (HR, 1.64; 95% confidence interval (CI), 1.15 to 2.35 based on only 216 of the 262 patients), by smoking (HR, 1.60; 95% CI 1.05 to 2.42), and by persistence of a large goiter (HR, 1.30; 95% CI, 1.05 to 1.61 based on only 248 patients), whereas the genotyping, based on the total number of risk alleles, had an HR of 1.30 (95% CI, 1.09 to 1.56). Furthermore, 5 of the 10 patients who had no risk alleles still had a relapse. In

patients 40 years of age or older, the only independent predictor was persistent goiter (HR, 1.56; 95% CI, 1.09 to 2.22), whereas in those younger than 40, a persistently high TRAb (HR, 1.93; 95% CI, 1.22 to 3.06) and the number of risk alleles (HR, 1.24; 95% CI, 1.01 to 1.53) were the only independent risk factors.

Conclusions

The best predictor of relapse after stopping antithyroid drug treatment was a persistently positive TRAb, followed in order by current smoking, a persistent goiter, and the number of risk SNPs in CTLA4 and CD40. However—perhaps because the number of patients was too small—for those younger than 40 years of age, a persistent TRAb and/or the number of risk SNPs were the only independent predictors, whereas for those 40 or older, a persistent goiter was the only independent predictor.

ANALYSIS AND COMMENTARY ● ● ● ● ●

If an individual has G/G at rs231775 in CTLA4, an increased risk of Graves' disease has now been confirmed in a variety of populations. Interestingly, G/G is three times more common in Asians in general, as compared with Caucasians. It will take years to sort out how SNPs present in hundreds of genes involved in immunity interact in different autoimmune conditions. Just considering CTLA4, the relative importance of different SNPs in susceptibility to Graves' disease varies substantially by geographic region (1). G/G alleles at rs231775 were first reported to be more common in Japanese patients with Graves' disease whose TSHR stimulating and/or blocking activities did not disappear within 5 years of treatment, as compared with patients in whom those activities had disappeared (2). However, this observation was not associated with risk of relapse (2). Some have reported that G/G at rs231775 is not useful for predicting remission versus relapse

within 1 year after discontinuing antithyroid drugs (3). The definition of "relapse," the specific details of antithyroid drug therapies used, and the duration of follow-up doubtless influence the relative importance of a candidate SNP for predicting relapse (indeed, the authors themselves disregarded SNPs that only predicted a relapse within 9 months or within 3 years).

The current study included "block-and-replace" (methimazole + levothyroxine treated) patients. This approach may be useful for patients in whom the balance of blocking versus stimulating TSHR antibody activity is shifting. It therefore would have been interesting to know the results of a TSHR antibody assay that only detected stimulating activity, in addition to the "TS-AB" assay used in the current paper, which measured both TSHR blocking and stimulating antibodies.

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Although the importance of a given SNP can vary substantially based on the region and the genetic makeup of a given population, SNPs surely will be found that either consistently increase the risk of relapse, or else actually protect a patient from relapse. Eventually, such testing may be available to doctors before they need to decide for or against starting a course of antithyroid drugs, but it does not seem likely that a few magic SNPs will turn out to be

the most important predictors of risk.

Meanwhile, for the practicing thyroidologist, the most interesting idea raised by this paper is a possible therapeutic intervention. Getting a patient to stop smoking is clearly important for reducing the risk of orbitopathy; maybe it reduces the risk of relapse after stopping antithyroid drugs as well.

References

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