



HYPERTHYROIDISM

Can we predict which patients with hyperthyroidism will develop agranulocytosis with antithyroid drugs?

BACKGROUND

Graves' disease is the most common type of hyperthyroidism in the United States. Antithyroid drugs (ATDs) are frequently used to treat Graves' disease. These drugs (Methimazole and Propylthiouracil in the United States, Carbimazole in Europe) are usually very well tolerated. However, agranulocytosis (low white blood cells) is a rare complication of ATDs occurring in 0.1-0.3% of patients. White blood cells (WBCs) help fight infections, so agranulocytosis can result in severe and even deadly infections. Presenting symptoms include sore throat, fever, and muscle aches, but severe infections occur in approximately two out of three patients and up to 5% of these patients will die of this complication.

The mechanism through which antithyroid drugs cause agranulocytosis is currently unknown, but studies suggest an autoimmune cause. Certainly, if patients at risk for this severe side effect could be identified, other options for treatment such as surgery or radioactive iodine could be chosen. Molecular tests have been used to identify patients at risk for other medical disorders and have been used in some patients with agranulocytosis. Previous studies have shown that certain genetic variants are associated with a high risk of antithyroid drug-induced agranulocytosis in ethnic Chinese people in Taiwan and Hong Kong. They analyzed molecular markers known as single-nucleotide polymorphisms (SNPs) in their study.

The Cheung study used SNPs to examine whether a specific genetic marker was associated with antithyroid drug-induced agranulocytosis in a population of ethnic Chinese people. The Hallberg study used SNPs to examine whether a similar pattern of genetic variants are associated with agranulocytosis in a European population.

THE FULL ARTICLE TITLE

Cheung CL et al. HLA-B*38:02:01 predicts carbimazole/methimazole-induced agranulocytosis. *Clin Pharmacol Ther* 2016;99:555-61. Epub January 12, 2016.

SUMMARY OF THE STUDY

Since 2013 in specialist or regional hospitals in Hong

Kong, agranulocytosis was found to have developed in 19 female and 5 male Chinese patients with Graves' disease. Genetic studies were performed on 24 of these patients. Agranulocytosis developed in 19 patients taking methimazole or carbimazole and in 5 patients taking. Controls (those without thyroid disease or agranulocytosis) included 387 randomly selected women from various other studies as well as an additional group of 57 patients with Graves' disease who had been treated with methimazole or carbimazole for at least 3 months without agranulocytosis.

The initial discovery screen detected a strong signal known as SNP rs185386680(G) in the HLA region. This identified HLA-B*38:02:01 variant is a susceptibility locus for agranulocytosis. Further, they found that HLA-DRB1*08:03 that had been found in the earlier studies did not meet the threshold for significance in this study.

THE FULL ARTICLE TITLE

Hallberg P et al for the EuDAC collaborators. Genetic variants associated with antithyroid drug-induced agranulocytosis: a genome-wide association study in a European population. *Lancet Diabetes Endocrinol* 2016;4:507-16. Epub May 3, 2016.

SUMMARY OF THE STUDY

Patients were recruited through national registries and hospitals collaborating in the European Drug-induced Agranulocytosis Consortium (EuDAC), a network of investigators in Sweden, Spain, France, Germany, the United Kingdom, and the Netherlands. Cases included patients in whom agranulocytosis developed during antithyroid drug treatment or within 7 days after stopping treatment. Each patient was required to have complete recovery after stopping of the drug. A total of 39 patients had agranulocytosis that was induced by antithyroid drugs (methimazole, 74%; carbimazole, 13%; and propylthiouracil, 13%). Researchers selected 5170 controls (people without agranulocytosis) from several Swedish national registries. In addition, 49 patients who had been treated for hyperthyroidism without developing agranulocytosis were selected. Roughly 600,000 SNPs were genotyped for final analyses.



HYPERTHYROIDISM, continued

The results identified three genetic variants to be associated with antithyroid-induced agranulocytosis: rs652888 located in an intron of EHMT2, HLA-B*27:05 and HLA-B*08:01. The predictive ability for all three variants combined was high. Using this analysis, the authors concluded that one case of antithyroid-induced agranulocytosis would be avoided for each 238 patients genotyped.

these variants would help choose the best treatment for Graves' disease. However, at present, these markers are not ready to be put into general clinical use but suggest that this may be the case in the future. Further, these studies provide information that may help to determine what causes antithyroid-induced agranulocytosis.

— Alan P. Farwell, MD, FACE

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

These two studies present preliminary information that patients that have certain genetic variants are at increased risk for antithyroid-induced agranulocytosis. Screening for

ATA THYROID BROCHURE LINKS

Hyperthyroidism: <http://www.thyroid.org/hyperthyroidism/>

Graves' disease: <http://www.thyroid.org/graves-disease/>

ABBREVIATIONS & DEFINITIONS

Agranulocytosis: a marked decrease in the white blood cell count that causes a patient to be more likely to develop an infection. This is commonly associated with a fever and/or a sore throat.

White blood cells: the infection-fighting cells of the blood.

Graves' disease: the most common cause of hyperthyroidism in the United States. It is caused by antibodies that attack the thyroid and turn it on.

Methimazole: an antithyroid medication that blocks the thyroid from making thyroid hormone. Methimazole is used to treat hyperthyroidism, especially when it is caused by Graves' disease.

Propylthiouracil (PTU): an antithyroid medication that blocks the thyroid from making thyroid hormone. Propylthiouracil is used to treat hyperthyroidism, especially in women during pregnancy.



American Thyroid Association (ATA)
Spring 2017 Satellite Symposium

Hypothyroidism - Where Are We Now?

Friday, March 31, 2017, 1:00 PM – 5:30 PM
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