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PROLONGED THERAPY WITH CARBIMAZOLE LEADS TO A 50% REMISSION RATE FOR GRAVES' DISEASE IN CHILDREN

Léger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C. **French Childhood Graves' Disease Study Group. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study.** J Clin Endocrinol Metab. October 26, 2011 [Epub ahead of print].

SUMMARY

BACKGROUND

The optimal therapy for Graves' disease in children is controversial. The remission rate with a single course of antithyroid drug is less than 30%. For this reason, many children are treated by either radiodiodine-131 (^{131}I) or surgical thyroidectomy as "definitive therapy." The policy for treatment varies among pediatric endocrinologists and institutions. The purpose of the current study was to assess the effect of the duration of carbimazole therapy on the remission of Graves' disease (GD) after three consecutive courses of carbimazole with discontinuation of the therapy after each course.

METHODS

This is a prospective study of 154 patients with GD up to age 18 in a multicenter French network. Each of the three treatment cycles with carbimazole lasted 2 years. The outcome after each course of carbimazole therapy was either relapse or remission based on follow-up for at least 18 months. If the patient relapsed, another course of therapy was begun, or if the patient and family preferred, definitive therapy was offered. Various demographic, clinical, and laboratory tests pertaining to thyroid function were performed. The variables associated with remission were analyzed with a regression model. These variables included age, sex, ethnicity, weight, height, body-mass index, pubertal stage, personal history of overt autoimmunity and susceptibility factors, family history of hyperthyroidism, severe initial clinical presentation, goiter, free thyroxine (T_4), free triiodothyronine, thyrotropin-receptor antibodies, and thyroid peroxidase autoantibodies.

RESULTS

The median duration of follow-up was 10.4 years. The mean age at presentation was about 12 years. Three serious adverse events occurred: allergic reaction, neutropenia, and arthralgia. The estimated remission rates 18 months after the withdrawal of antithyroid drug treatment increased with time and were 20% (95% confidence interval [CI], 13 to 26), 37% (95% CI, 29 to 45), 45% (95% CI, 35 to 54), and 49% (95% CI, 40 to 57%) after 4, 6, 8, and 10 years of follow-up, respectively. After 10 years follow-up, the estimated percentage of patients still receiving carbimazole was 11% and the percentage receiving definitive therapy was 36%. There was a positive effect on treatment of less severe forms of hyperthyroidism (free T_4, <35 pmol/L [2.7 ng/dl]). Age greater than 10 years at diagnosis was an independent predictor of definitive treatment (hazard ratio, 2.46; 95% CI, 1.12 to 5.40; P = 0.02). The presence of other autoimmune diseases increased the possibility of remission twofold but also predicted a longer duration of medical treatment.

CONCLUSIONS

About half the patients achieved remission after discontinuing carbimazole. There was a plateau in the incidence of remission achieved after 8 to 10 years of antithyroid drug therapy.

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ANALYSIS AND COMMENTARY

The best treatment of children with Graves' disease has been controversial for many years. The current study more or less confirms the findings reported from the UCLA Pediatric Endocrine Division in 1987; namely, that remission rates in children and adolescents treated with antithyroid drugs increased by 25% for every additional 2 years of treatment (1). The relatively low prevalence of Graves' disease in children, no more than 1 in 10,000 in the United States, makes it difficult to do randomized studies of different therapeutic regimens (3). Therefore, it is reassuring that this multicenter prospective study in France showed the efficacy of antithyroid drug therapy of children and reassured us that patience and a long-range outlook is a virtue in their treatment because remission increases with time. We now know that propylthiouracil is hazardous in this age group because it is associated with severe hepatotoxicity, but this does not occur with methimazole and presumably carbimazole that is converted into methimazole in vivo (2).

The high prevalence of 50% remission after 10 years of treatment found in this study is greater than the 15% to 30% remission reported in a recent review, although this lower percentage is consistent with 4 years of therapy (3). Although surgery has been recommended for children younger than 10 years of age, it has complications not found with radioiodine, such as hypoparathyroidism and recurrent laryngeal-nerve paralysis. Both of the definitive therapies usually cause permanent hypothyroidism, a complication not found with antithyroid drug therapy that usually leaves the thyroid gland intact. In fact, the pendulum has swung toward using a dose of ^{131}I that ablates the thyroid, even in children, leading to lifelong therapy with thyroid hormone (3), an outcome that I do not consider optimal.

— Jerome M. Hershman, MD

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