The risk of hyperthyroidism relapse following antithyroid drug withdrawal in children with Graves' disease can be decreased only by a longer initial duration of therapy

Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P, Leger J. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. J Clin Endocrinol Metab 2008;93:3817-26

SUMMARY

BACKGROUND Predicting the outcome of antithyroid drug therapy (ATD) for Graves' disease is problematic. There are many retrospective studies in adults showing that patients with more severe degrees of hyperthyroidism, large goiters, a high triiodothyronine (T_3)-to-thyroxine (T_4) ratio, and higher levels of anti-thyrotropin (TSH) receptor antibodies (TRAb) are less likely to have a remission than are patients with milder disease and smaller goiters. Yet none of these features accurately predict outcome. In children there is even more uncertainty about factors that predict outcome. Such studies in children are limited. As a result, there is debate concerning how Graves' disease in children should be treated. The aim of this study was to identify factors that predict relapse of hyperthyroidism in children with Graves' disease treated with ATDs.

METHODS This was a prospective, multicenter cohort study of children with Graves' disease treated with carbimazole. The intention was to treat all patients for a total of 24±3 months. All consecutive patients with Graves' hyperthyroidism who were younger than 18 years of age were included in the study, but children with neonatal hyperthyroidism were excluded. The diagnosis was based on clinical signs of hyperthyroidism, a TSH <0.05 μIU/ml, and a serum free T_4 (FT_4) >21 pmol/L (1.6 ng/dl) with or without a serum free T_3 (FT_3) >11 pmol/L (0.71 ng/dl) and the presence of significant serum TRAb levels with or without serum antithyroid peroxidase antibodies. The intent was to treat all patients with one or two daily doses of carbimazole at a starting dose of 0.5 mg/kg/day, but over time this was decreased by 20 to 40% to maintain euthyroidism. The primary outcome was relapse of hyperthyroidism. Patients had clinical evaluations at months 1, 2, 3, 6, 9, 12, 18, and 24.

RESULTS A total of 154 children were initially included; 17 (11%) were 5 years of age or younger and 137 (89%) were older than 5 years; 118 were female (77%), 36 were male (23%), and 65 were prepubertal (47%). Serum TRAb levels were significantly higher in patients younger than 5 years than in older patients (P<0.0001); they were also higher in patients with a severe initial clinical presentation as compared with those without a clinically severe presentation (P = 0.03). Serum TRAb and FT_3 levels were significantly correlated (P = 0.005) but there was no correlation between TRAb levels and goiter size or gender. Most patients (147; 95%) completed one course of therapy. Seven patients who did not complete one course of ATDs were excluded from the analysis. The median duration of ATD treatment was 25 months (range, 23 to 28), but only 83 patients (56%) received ATDs according to the protocol for 21 to 27 months. A total of 64 children (44%) had deviations from the study protocol and 20 received antithyroid drugs for 12 to 20 months because of noncompliance; 44 patients received ATDs for more than 27 months. Overall, the estimated rate of hyperthyroidism relapse was 59% (95% confidence interval [CI], 52 to 67) at 1 year and 68% (95% CI, 60 to 76) at 2 years after the end of treatment (Figure 1). The median time to relapse was 8 months (95% CI, 5.4 to 11.4). In all, 64 of the 99 relapses (65%) occurred in the first 6 months and 87 of the 99 (88%) relapses occurred in the first year (Figure 1).

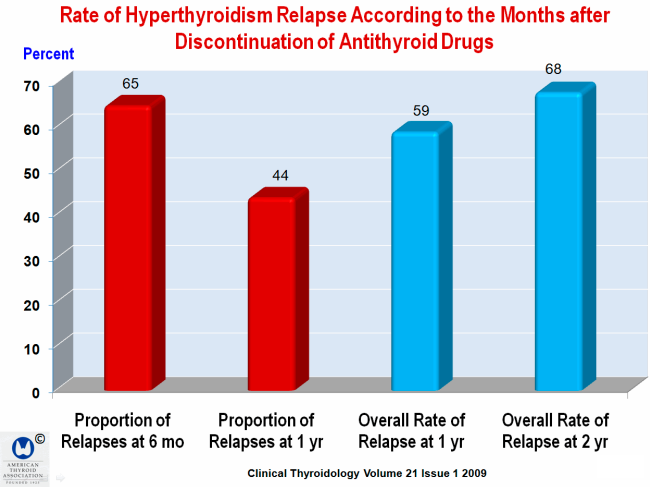

Figure 1. This shows the proportion of the 99 relapses of hyperthyroidism that occurred at 6 months and 1 year after the end of antithyroid drug treatment, and the overall rates of relapse at 1 and 2 years after antithyroid drug treatment. The median time to relapse was 8 months (95% CI 5.4 to 11.4 months). Derived from Kaguelidou et al data.

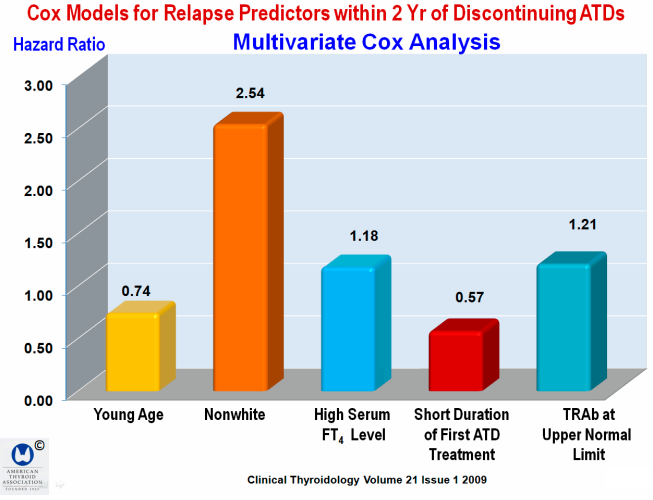

Figure 2. The results of a multivariate Cox analysis within 2 years of discontinuing ATDs. Derived from data in Table 2 by Kaguelidou et al.

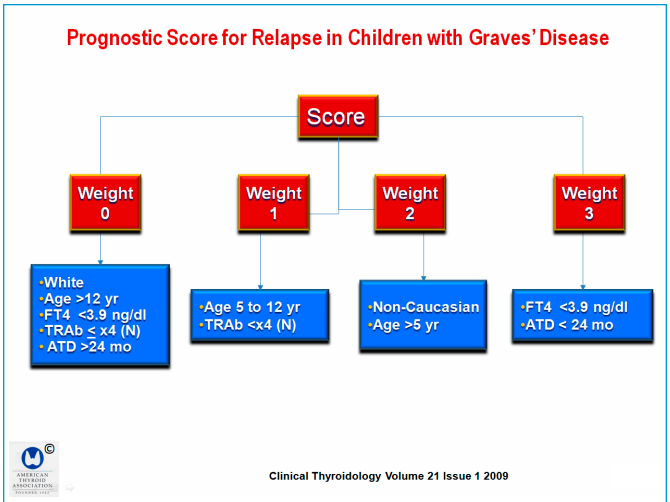

Figure 3. The prognostic scoring system devised by Kaguelidou et al. is derived from the results of this study. The data are derived from Table 3.

Five variables were identified as independent predictors of relapse in a multivariate Cox model: (1) patient age (hazard ratio [HR], 0.74; 95% CI, 0.56 to 0.97; P = 0.05); (2) nonwhite patients (HR, 2.54; 95% C,I 1.50 to 4.3; P = 0.0003; (3) serum FT_4 levels (HR, 1.18; CI, 1.07 to 1.30; P<0.0001); (4) duration of the first course of ATD treatment (HR, 0.57; 95% CI, 0.39 to 0.84; P = 0.007); (5) upper normal limit for TRAB concentration (HR, 1.21; 95% CI, 1.02 to 1.45; P<0.0001 (Figure 2). Older children were less likely to experience a relapse of hyperthyroidism after ATD withdrawal, with a decrease in risk of 26% for every 5-year increase in age. Nonwhite patients were found to be 2.5-fold more likely to suffer a relapse than white patients. Also, a 10-point increase in serum FT_4 and a 10-unit increase in the multiple of upper normal limit for serum TRAb levels at diagnosis resulted in an 18% and a 21% increase of relapse risk, respectively. A prognostic score, which was derived from the regression coefficient of each variable retained in the final model, is shown in Figure 3.

CONCLUSION The risk of relapse of hyperthyroidism after antithyroid drug withdrawal in children with Graves' disease can be decreased only by a longer initial duration of antithyroid drug therapy

COMMENTARY

The principle finding in this study is that five independent variables (Figure 2) had a significant effect on the recurrence rates in children with Graves' hyperthyroidism. As a practical matter, however, the only variable that might be amenable to clinical manipulation is the duration of ATD therapy. The authors suggest that long courses of ATD are associated with a better-than-usual outcome, but acknowledge that their study was not designed to answer just how long ATD therapy should be continued. The study did, nonetheless, find that every additional year of treatment was associated with a decrease in the rate of relapses.

In adults with Graves' hyperthyroidism, ATD treatment for 12 to 18 months is the usual practice (1, 2). The evidence that prolonging ATD therapy improves the relapse rates of Graves' hyperthyroidism is inconsistent. One prospective randomized trial found that after 2 years of follow-up, there was significant improvement in the hyperthyroidism relapse rate when patients were treated with ATDs for 18 months, as compared with only 6 months (42% vs. 62%, P<0.05) (3). Another study found, after a 2-year follow-up, that relapse rates were 46% in patients treated with ATDs for 12 months and 54% in those treated for 24 months (P = 0.36); however, after a 5-year follow-up, the relapse rates were almost identical after 12 and 24 months of ATD treatment (83 vs. 86%, P = 0.7) (4). Still another prospective study, which compared the relapse rates of Graves' hyperthyroidism in patients treated for either 42 or 18 months, found the relapse rates after 2 years of follow-up were 36% and 29% (P not significant) in the two groups, respectively (5). An evidence-based study of the literature found that the optimal duration of ATD therapy is 12 to 18 months (6). A multicenter European trial found that the dose of methimazole in Graves' disease can safely be kept to the minimal required dose, which will provide the same chance of remission as higher doses, thus resulting in the best balance of risk and benefit (7).

The other uncertainty in the management of hyperthyroid children is compliance. The evidence suggests that treatment adherence is generally lower in children than in adults, particularly in adolescents as they approach the age of independence (8). With this aside, relapse of Graves' hyperthyroidism in children poses a substantial health problem that requires ongoing study such as the important study by Kaguelidou et al.

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