BLOCK-REPLACEMENT TREATMENT OF HYPERTHYROIDISM MAY BE USEFUL IN GRAVES' ORBITOPATHY

Elbers L, Mourits M, and Wiersinga W. **Outcome of very long-term treatment with antithyroid drugs in Graves' hyperthyroidism associated with graves' orbitopathy.** Thyroid, December 29, 2011. doi: 10.1089/thy.2010.0181

SUMMARY

BACKGROUND

Antithyroid drugs are generally used to treat Graves' hyperthyroidism in one of two ways: 1) to completely block the synthesis of thyroid hormone while also replacing thyroid hormone, or 2) to titrate the dose of antithyroid drug to maintain just enough hormone synthesis to keep the patient euthyroid. Randomized trials of the titration approach have shown that if the drugs are discontinued after only 6 months, Graves' hyperthyroidism recurs in the following year more often than if drugs are continued for 12 months: continuing the drugs for more than 18 months is not more effective. These studies did not address how orbitopathy responded. Over the past 50 years, however, numerous uncontrolled retrospective studies have indicated that using antithyroid drug therapy for longer periods is associated with lower rates of recurrent hyperthyroidism. This perception is supported by the current retrospective study, which used the blocking/replacement approach for patients with moderate-to-severe orbitopathy until the orbitopathy needed no further treatment, which generally took at least 2 years.

METHODS

All 255 patients who had been referred to the Orbital Center of the Academic Medical Center in Amsterdam for Graves' orbitopathy between 1995 and 2005 were sent a questionnaire. Of these 255 patients, 114 returned the questionnaire: 28 were excluded because their local endocrinologist had changed the treatment method, 10 did not provide sufficient data, and 3 had not given informed consent, leaving 73 patients for the study. The patients were given a constant dose of antithyroid drug (generally, 30 mg of methimazole) plus thyroxine replacement, and the regimen was stopped only when no further medical and surgical treatment was required for Graves' ophthalmopathy other than eye lubricants (median treatment period, 3.5 years, range, 2 to 12). About 30% of patients remained active smokers at the time that the antithyroid regimen was discontinued. The majority of the patients had undergone orbital decompression surgery, almost half had undergone irradiation and eyelid surgery, about 45% had received glucocorticoids, and about 40% had undergone eye muscle surgery. Only about 10% had received none of these treatments for their orbitopathy.

RESULTS

Hyperthyroidism did not recur in 46 patients (63%) after medical treatment was stopped (mean follow-up, 51 months; range, 12 to 124). Of the 27 patients (37%) who did have recurrence of hyperthyroidism (median time to recurrence, 3 months; range, 1 to 65), 19 were then treated with radioactive iodine (^{131}I); in the remaining 8, antithyroid drug treatment was restarted. These 27 patients were subsequently followed for mean periods of 69 and 30 months, respectively. Two patients indicated on their questionnaires that they had some worsening of eye symptoms after they had stopped antithyroid drugs, although a review of their records did not substantiate physical worsening of their Graves' ophthalmopathy. Otherwise, there was no worsening of ophthalmopathy in any of the 73 patients, regardless of whether they were in the group that had a recurrence of Graves' hyperthyroidism (median follow-up, 63 months; range, 12 to 170) or not (median follow-up, 51 months; range, 12 to 124).

CONCLUSIONS

The recurrence rate of 37% is less than what has generally been reported in studies with shorter periods of antithyroid drug treatment and with shorter periods of follow-up. No differences in clinical or lab tests were detected between the group that had recurrent hyperthyroidism and the group in whom hyperthyroidism did not recur. No substantial worsening of Graves' orbitopathy was observed, even in the 19 patients whose recurrent hyperthyroidism was treated with ^{131}I.

COMMENTARY

None of the patients did, in fact, require further orbital therapy, which confirms the expertise of this group. Although patient questionnaires were initially used, the responses were confirmed by contacting the specialists treating the patients if the patients were no longer being followed at the Orbital Center. Nonetheless, only about a third of patients invited to participate were finally included. Some were excluded because their thyroid disease had been "prematurely" treated with radioactive iodine or thyroidectomy; presumably none of these cases was resistant to the antithyroid drug regimen. Despite these potential drawbacks to the study, several facts support the concept that prolonged antithyroid treatment can reduce recurrences: (1) Graves' disease will eventually burn out in many patients, (2) thyroid-stimulating immunoglobulin levels do tend to drop following treatment with antithyroid drugs (or surgery), (3) certain thionamides appear to have immunosuppressive properties, and (4) some of the risk factors for a relapse of Graves' hyperthyroidism are also associated with increased risk of progression of Graves' ophthalmopathy (e.g., smoking and goiter size). If more specific TSH receptor antibodies correlate consistently with the activity of orbitopathy (1), they could prove useful in determining when to perform reconstructive orbital surgery and/or discontinue antithyroid drug therapy.

— Stephen W. Spaulding, MD

REFERENCE

1. Lytton SD, Ponto KA, Kanitz M, et al. A novel thyroid stimulating immunoglobulin bioassay is a functional indicator of activity and severity of Graves' orbitopathy J Clin Endocrinol Metab 2010;95: 2123-31.