Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION FOUNDED 1923

Stimulating the Uptake of ^{131}I in Multinodular Goiter by Pretreatment with Recombinant Human TSH Improves Patient Outcomes at 5 Years

Fast S, Nielsen VE, Grupe P, Boel-Jørgensen H, Bastholt J, Andersen PB, Bonnema SJ, Hegedüs L. Prestimulation with recombinant human thyrotropin (rhTSH) improves the long-term outcome of radioiodine therapy for multinodular nontoxic goiter. J Clin Endocrinol Metab. May 10, 2012 [Epub ahead of print]. doi:10.1210/jc.2011-3335.

SUMMARY

BACKGROUND

If obstructive signs or symptoms develop in a patient with multinodular goiter (MNG)—and the surgical risk is deemed acceptable—surgery at a major referral hospital is the treatment of choice (hyperthyroidism, if present, is usually treated first). If surgery is not feasible, ^{131}I can be given to reduce goiter size somewhat, although it initially may cause thyroid swelling and increase the release of thyroid hormone, potentially significant side effects. If the goiter is very large or its uptake is low, large doses of ^{131}I may be required, increasing whole-body radiation and possibly involving the expense of hospitalization. To try to enhance the effectiveness of ^{131}I, a number of centers have tried recombinant human TSH (rhTSH) on an experimental basis. It is given a day before ^{131}I treatment, which increases the uptake of ^{131}I in areas of the gland where uptake is low, makes the radiation more uniform, and increases the retention of ^{131}I in the thyroid. It also increases long-term hypothyroidism. The current paper reports 5-year outcome data from two previously published randomized, double-blind, placebo-controlled studies on selected patients with MNG from an area of Denmark where iodine intake is moderately deficient (1,2).

METHODS

One of the two earlier papers addressed the effects of rhTSH on patients with goiters <100 ml (measured by ultrasound), while the other paper focused on patients with goiters >100 ml (by MRI). Half the patients in both studies received an injection of 0.3 mg of rhTSH 24 hours before ^{131}I was given, while the other half received a placebo injection. The inclusion and exclusion criteria between the two studies differed substantially, as did the ^{131}I doses given. In the first study (1), out of 712 consecutive patents seen from 2002 to 2004 who had "nontoxic" MNG, 57 patients met a variety of inclusion criteria, including having an ^{131}I uptake of 20% or greater, whereas 99 patients with uptakes less than 20% were excluded. Almost half the patients in this study were subclinically hyperthyroid (TSH <0.1 mU/ml). The ^{131}I dose was calculated based on the estimated thyroid volume and the effective ^{131}I half-life: the median dose was 14 mCi in the placebo group and 15.7 mCi in the rhTSH group (the highest dose permitted was 16.2 mCi). After 1 year, the goiters in the placebo group had shrunk by 46%, while those in the rhTSH group had shrunk by 62% (P<0.002). The incidence of hypothyroidism was 5 times greater in the latter patients, who also had 3 times as many adverse events, especially transient hyperthyroidism and cervical discomfort or pain. In the second study, 29 patients with very large nodular goiters who could not or would not undergo surgery were studied (2). Five of the patients had frank hyperthyroidism and were given methimazole until 8 days before the ^{131}I treatment. The patients' mean baseline 24-hour ^{131}I uptake was about 35%, and the mean TSH was about 0.2 mU/L. The median ^{131}I treatment dose was 41 mCi in the placebo group and was 37 mCi in the rhTSH group. (Two patients in the latter group had their ^{131}I doses restricted to 100 mCi.) After 1 year, the goiters in the placebo group had shrunk from

continued on next page

170 ml to 121 ml, while those in the rhTSH group had shrunk from 151 ml to 72 ml. Two patients given rhTSH required 25 mg of prednisolone for thyroid swelling and tenderness, and one was admitted to the hospital for stridor. Only 2 of 14 in the rhTSH group had no adverse events, whereas 7 of 15 in the placebo group had no adverse events. Hypothyroidism had developed in 1 of 15 patients given placebo and in 3 of 14 patients given rhTSH.

RESULTS

Follow-up data were available on 80 of the 86 patients from the two studies. When the data were combined, the placebo groups' goiters had shrunk another 13% and the rhTSH groups' goiters had shrunk another 10% after 5 years. "Treatment failures" (cases in which patients required subsequent thyroid surgery or additional ^{131}I treatment) were twice as common in the patients with the large goiters as in those with goiters <100 ml. In the combined placebo groups, 20% (9 of 44) needed additional treatment (surgery in 6, and additional ^{131}I in 3), whereas in the rhTSH groups, only 5% (2 of 42) needed surgery (P<0.02). Since more of the patients receiving placebo needed additional therapy, their mean follow-up period was slightly shorter (65 months) than that for the rhTSH groups (73 months). On a yes/no question concerning overall satisfaction with the initial therapy: 90% of those who had been given rhTSH and 69% of those given placebo answered "yes"(P = 0.025).

CONCLUSIONS

Five years after treating two highly selected groups of patients with ^{131}I, patients with MNG who were also given rhTSH had fewer goiter-related symptoms, fewer of them needed additional therapy, and their satisfaction with the initial therapy was higher. The goiter shrinkage remained superior, but the incidence of hypothyroidism was much greater in those who received rhTSH.

ANALYSIS AND COMMENTARY

The title of the article indicates that only patients with "nontoxic" MNGs were studied, but many patients had subclinical or frank hyperthyroidism. All the patients had a basal ^{131}I uptake of 20% or greater, so their autonomous nodules probably were more active than those in patients with a lower ^{131}I uptake. However, there are many patients with MNG with a ^{131}I uptake less than 20%, so it would be interesting to know whether such patients would also respond to rhTSH in this Danish population. Although the data do not address that question directly, several recent smaller studies from Brazil—where iodine intake from 1998 to 2003 was excessive—obtained similar results. These studies used substantially lower doses of rhTSH (≤0.1 mg), and the patients' ^{131}I uptakes were below 20%, even after being on low-iodine diets. A study of 28 patients with MNG (average volume >100 ml by helical CT) who had subclinical hyperthyroidism were treated with methimazole for 3 months (3). The methimazole was discontinued 2 weeks before measuring the basal RAI uptake (which generally remained under 20%), and methimazole was discontinued again for 2 weeks preceding the dose of 30 mCi ^{131}I. The decrease in thyroid volume was about 40% at 2 years, as compared with a 15% decrease (statistically insignificant) in patients receiving placebo. A different study on 22 patients with MNG who were euthyroid (none with basal TSH levels below 0.21 mU/ml), who ate a low-iodine diet for 2 weeks before getting 30 mCi ^{131}I, obtained similar results (4). After 1 year, the goiters had shrunk almost 40%, either with a dose of 0.01 mg or 0.1 mg of rhTSH.

Overall, giving rhTSH to patients with MNG seems to double the 24-hour uptake of ^{131}I, regardless of whether the rhTSH dose is 0.01 mg or 0.9 mg. In

continued on next page

contrast, both thyroid swelling and thyroid-hormone levels increase as the rhTSH dose increases from 0.1 mg to 0.9 mg in normal subjects (5). Indeed, a more recent study from the same Danish group did use a lower dose of rhTSH (0.1 mg) and showed that it enhances the efficacy of ^{131}I in shrinking goiters more than threefold (6). Given that there is continuing restriction in the availability of rhTSH, and recognizing that it is about 10,000 times more valuable than gold, it would seem appropriate on both clinical and financial grounds to use a smaller dose than the 0.3 mg used in the pair of studies analyzed by the current study. A recent study showed that if rhTSH is reconstituted in PBS containing BSA, its in vitro biologic activity is stable for at least 6 months (7).

It is also worth noting that several other ways to increase the ^{131}I uptake/retention in MNG have been reported. These include: (1) pretreating patients with methimazole to raise TSH levels, then discontinuing the methimazole before the ^{131}I treatment, as mentioned above; (2) giving lithium before and after ^{131}I (8,9); and (3) giving nonradioactive ^{127}I after ^{131}I treatment (10).

— Stephen W. Spaulding, MD

REFERENCES

1. Nielsen VE, Bonnema SJ, Boel-Jørgensen H, Grupe P, Hegedüs L. Stimulation with 0.3-mg recombinant human thyrotropin prior to iodine 131 therapy to improve the size reduction of benign nontoxic nodular goiter: a prospective randomized double-blind trial. Arch Intern Med 2006;166:1476-82.
2. Bonnema SJ, Nielsen VE, Boel-Jørgensen H, Grupe P, Andersen PB, Bastholt J, Hegedüs L. Improvement of goiter volume reduction after 0.3 mg recombinant human thyrotropin-stimulated radioiodine therapy in patients with a very large goiter: a double-blinded, randomized trial. J Clin Endocrinol Metab 2007;92:3424-8. Epub June 12, 2007.
3. Cubas ER, Paz-Filho GJ, Olandoski M, Goedert CA, Woellner LC, Carvalho GA, Graf H. Recombinant human TSH increases the efficacy of a fixed activity of radioiodine for treatment of multinodular goitre. Int J Clin Pract 2009;63:583-90. Epub September 18, 2008.
4. Albino CC, Graf H, Paz-Filho G, Diehl LA, Olandoski M, Sabbag A, Buchpiguel C. Radioiodine plus recombinant human thyrotropin do not cause acute airway compression and are effective in reducing multinodular goiter. Braz J Med Biol Res 2010;43:303-9.
5. Fast S, Nielsen VE, Bonnema SJ, Hegedüs L. Dose-dependent acute effects of recombinant human TSH (rhTSH) on thyroid size and function: comparison of 0.1, 0.3 and 0.9 mg of rhTSH. Clin Endocrinol (Oxf) 2010;72:411-6. Epub June 8, 2009.
6. Fast S, Hegedüs L, Grupe P, Nielsen VE, Bluhme C, Bastholt L, Bonnema SJ. Recombinant human thyrotropin-stimulated radioiodine therapy of nodular goiter allows major reduction of the radiation burden with retained efficacy. J Clin Endocrinol Metab 2010;95:3719-25. Epub June 2, 2010.
7. Lin R, Hogen V, Cannon S, Marion KM, Fenton MS, Hershman JM. Stability of recombinant human thyrotropin potency based on bioassay in FRTL-5 cells. Thyroid 2010;20:1139-43.
8. Płazińska MT, Królicki L, Bąk M. Lithium carbonate pre-treatment in 131-I therapy of hyperthyroidism. Nucl Med Rev Cent East Eur 2011;14: 3-8.

continued on next page

9. Martin NM, Patel M, Nijher GM, Misra S, Murphy E, Meeran K. Adjuvant lithium improves the efficacy of radioactive iodine treatment in Graves' and toxic nodular disease. Clin Endocrinol (Oxf). March 24, 2012 [E-pub ahead of print]. doi:10.1111/j.1365-2265.2012.04385.x.

10. Rogowski F, Abdelrazek S, Szumowski P, Zonenberg A, Parfienczyk A, Sawicka A. The influence of non-radioactive iodine (^{127}I) on the outcome of radioiodine (^{131}I) therapy in patients with Graves' disease and toxic nodular goitre. Nucl Med Rev Cent East Eur 2011;14:9-15.