MODIFIED-RELEASE RECOMBINANT HUMAN TSH AUGMENTS THE EFFECT OF ^{131}I THERAPY IN BENIGN MULTINODULAR GOITER

Graf H, Fast S, Pacini F, Pinchera A, Leung A, Vaisman M, Reiners C, Wemeau JL, Huysmans D, Harper W, Driedger A, Noemberg de Souza H, Castagna MG, Antonangeli L, Braverman L, Corbo R, Düren C, Proust-Lemoine E, Edelbroek MA, Marriott C, Rachinsky I, Grupe P, Watt T, Magner J, Hegedus L. **Modified-release recombinant human TSH (MRrhTSH) augments the effect of ^{131}I therapy in benign multinodular goiter: results from a multicenter international, randomized, placebo-controlled study.** J Clin Endocrinol Metab. February 23, 2011 [Epub ahead of print].

SUMMARY

BACKGROUND

Surgical thyroidectomy or radioiodine-131(^{131}I) are the treatments for multinodular goiters that cause compressive symptoms or cosmetic disfigurement. However, many multinodular goiters have a relatively low uptake of radioiodine, so that the dose of ^{131}I necessary for a good effect becomes very large. The purpose of this study was to determine whether modified recombinant thyrotropin (MRrhTSH) could be used to stimulate radioiodine uptake and result in an effective reduction of the goiter and an increase in the tracheal lumen.

METHODS

The criteria for inclusion in the study were a clinical diagnosis of multinodular goiter that was 40 to140 ml in size by ultrasound and palpation, normal total triiodothyronine (T_3) and thyroxine (T_4) levels, TSH that ranged from suppressed to the upper limit of normal, negative results on fine-needle aspiration for thyroid cancer, and a normal electrocardiogram. Thyroid volume was measured by computed tomography at baseline and repeated after ^{131}I therapy. Radioiodine uptake was measured at 24, 48, and 120 to 168 hours. The ^{131}I dose was calculated to deliver 100 Gy to the thyroid gland. Patients were randomly assigned to receive either placebo, 0.01 mg of MRrhTSH, or 0.03 mg of MRrhTSH 1 day before the dose of ^{131}I was administered. MRrhTSH contains the same active ingredient as rhTSH (Thyrogen) but is reconstituted in a different diluent (sodium carboxymethylcellulose) to provide a delayed maximum concentration. The study was an international phase 2 trial sponsored by Genzyme (Cambridge, MA). Free T_4, free T_4 index, total T_4, free T_3, total T_3, and TSH were measured on days 2, 5, 14, 30, 60, and 180. A thyroid quality-of-life questionnaire was performed at baseline and on days 5, 90, and 180.

RESULTS

Ninety-five patients were selected for the study: 32 in the placebo group, 30 in the 0.01-mg MRrhTSH group, and 33 in the 0.03 -mg MRrhTSH group. The ages ranged from 35 to 80 years. Serum TSH ranged from undetectable to the upper limit of normal. The mean 24-hour thyroid uptake was approximately 30% and did not differ among the three groups. The mean doses of ^{131}I varied ranged from 32 to 39 mCi, with

TABLE 1. Changes in Goiter Volume (GV) Comparing the Initial Volume and the Volume 6 Months after ^{131}I Therapy.*

Treatment	Initial GV (ml)	GV at 6 mo (ml)	% Reduction in GV	>28% Reduction in GV
Placebo	100±45	77±37	23±9	25%
0.01 mg of MRrhTSH	93±51	70±36	23±16	37%
0.03 mg of MRrhTSH	103±39	70±37	33±21	64%

*Values are means ±SD.

a range of 5 to 103 mCi. Table 1 shows the results of the study in regard to the reduction of goiter size. The 0.03-mg dose of MRrhTSH caused a greater percent reduction in goiter volume than occurred with the placebo or the 0.01-mg dose. A clinically significant response was defined as a 28% or greater reduction in goiter size based on the literature. This was achieved in a significantly higher percentage (64%) of patients receiving the 0.03-mg as dose compared with the other groups. The smallest cross section of the trachea increased in all groups, and the increase did not differ significantly between the groups.

The majority of patients became either subclinically hyperthyroid or overtly hyperthyroid during days 1 to 20 after the ^{131}I therapy, but there was no difference between groups. Overt hypothyroidism at day 180 was most common in the high-dose MRrhTSH group (24%) as compared with either placebo (6%) or the low-dose MRrhTSH (3%) group. Every subject reported improved quality of life relative to baseline, but there was no difference between groups. Adverse events related to increased thyroid hormone levels and hyperthyroidism were more common in the groups receiving MRrhTSH. Atrial fibrillation developed in one patient 15 days later. Transient neck pain was reported in the placebo (9.4%), low-dose MRrhTSH (10%), and high-dose MRrhTSH (18.1%) groups.

CONCLUSION

The dose of 0.03 mg of MRrhTSH significantly augmented the effect of ^{131}I on reduction of the volume of multinodular goiters.

COMMENTARY 1

In the United States, the preferred treatment is surgery for large compressive goiters with ^{131}I treatment as the alternative (1). There are several single-institution trials demonstrating that pretreatment with rhTSH improved goiter shrinkage (1-5). Considering the high cost for thyroidectomy, including the risk of thyroid hormone replacement (100%), hypoparathyroidism (0.5 to 2%), and recurrent laryngeal-nerve damage (0.5 to 2%) in the hands of an experienced thyroid surgeon, rhTSH-stimulated ablation should be considered a cost-effective, viable option, since the majority of patients do not become hypothyroid and there is no risk to the parathyroid glands and the recurrent laryngeal nerves. When MRrhTSH becomes available, this therapy should be considered as first-line alternative treatment for large nontoxic goiters. This international study suggests that the response to rhTSH-stimulated ablation is similar in patients from different genetic backgrounds and with different iodine intake in different countries. Nevertheless, my first choice will remain surgery for the large symptomatic nontoxic goiter, but I will look forward to additional trials for this new form of rhTSH.

— Stephanie L. Lee, MD, PhD

COMMENTARY 2

Since Huysmans pioneered the use of rhTSH to increase thyroid uptake of radioiodine, several groups have used rhTSH in single doses that range from 0.03 to 0.45 mg to increase the thyroid uptake of a therapeutic dose of radioiodine-131 in patients with nodular goiter in order to reduce goiter size and compressive symptoms (1-8). A dose of 0.03 mg of ordinary rhTSH resulted in similar goiter volume reduction and increase of the tracheal lumen that were achieved with 0.03 mg MRrhTSH (6). One side effect of this therapy for multinodular goiter is the development of Graves' hyperthyroidism in some patients (2).

I have used 0.1 mg of rhTSH to increase thyroid uptake of a therapeutic dose of ^{131}I in patients with subclinical hyperthyroidism and relatively low 24-hour radioiodine uptake. In general, the rhTSH causes a doubling of the 24-hour uptake of radioiodine, thus enabling the administration of a lower total dose of ^{131}I.

A study of the stability of rhTSH in regard to stimulating the uptake of radioiodine in cultured thyroid cells showed that rhTSH kept at 4°C, –11°C, –60°C, and room temperature maintained good biologic potency for more than 6 months of storage, indicating that the biologic activity is very stable (9). Recombinant TSH is provided in ampules containing 1.2 mg. If the material is allocated by your pharmacy into various vials after dilution and stored in the cold, it could be sufficient for treatment of many patients with multinodular goiter over a 6-month period. Lastly, it should be noted that this treatment of multinodular goiter is an off-label use of rhTSH.

— Jerome M. Hershman, MD

REFERENCES

1. Hegedus L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. Endocr Rev 2003;24:102-32.
2. Bonnema SJ, Hegedus L. A 30-year perspective on radioiodine therapy of benign nontoxic multinodular goiter. Curr Opin Endocrinol Diabetes Obes 12009;6:379-84.
3. Wesche MF, Tiel-V Buul MM, Lips P, Smits NJ, Wiersinga WM. A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. J Clin Endocrinol Metab 2001;86:998-1005.
4. Huysmans DA, Nieuwlaat WA, Erdtsieck RJ, Schellekens AP, Bus JW, Bravenboer B, Hermus AR. Administration of a single low dose of recombinant human thyrotropin significantly enhances thyroid radioiodide uptake in nontoxic nodular goiter. J Clin Endocrinol Metab 2000;85:3592-6.
5. Nieuwlaat WA, Huysmans DA, van den Bosch HC, Sweep CG, Ross HA, Corstens FH, Hermus AR. Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. J Clin Endocrinol Metab 2003;88:3121-9.
6. Silva MN, Rubio IG, Romao R, Gebrin EM, Buchpiguel C, Tomimori E, Camargo R, Cardia MS, Medeiros-Neto G. Administration of a single dose of recombinant human thyrotrophin enhances the efficacy of radioiodine treatment of large compressive multinodular goitres. Clin Endocrinol (Oxf) 2004;60:300-8.
7. Albino CC, Mesa CO Jr, Olandoski M, Ueda CE, Woellner LC, Goedert CA, Souza AM, Graf H. Recombinant human thyrotropin as adjuvant in the treatment of multinodular goiters with radioiodine. J Clin Endocrinol Metab 2005;90:2775-80.
8. Cohen O, Ilany J, Hoffman C, Olchovsky D, Dabhi S, Karasik A, Goshen E, Rotenberg G, Zwas ST. Low-dose recombinant human thyrotropin-aided radioiodine treatment of large, multinodular goiters in elderly patients. Eur J Endocrinol 2006;154:243-52.
9. 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.