Preparation for ^{131}I remnant ablation with 54 mCi is equally effective with thyroid hormone withdrawal and recombinant human TSH

Chianelli M, Todino V, Graziano FM, Panunzi C, Pace D, Guglielmi R, Signore A, Papini E. Low-activity (2.0 GBq; 54 mCi) radioiodine post-surgical remnant ablation in thyroid cancer: comparison between hormone withdrawal and use of rhTSH in low-risk patients. Eur J Endocrinol 2009;160:431-6.

SUMMARY

BACKGROUND Thyroid remnant ablation after total thyroidectomy has traditionally been performed after thyroid hormone withdrawal (THW). However, the subsequent hypothyroidism frequently causes fatigue, depression, difficulties with concentration, and myriad other debilitating symptoms. Thus, the development of recombinant human TSH (rhTSH) was well received by patients with thyroid cancer and their clinicians, as it offered the opportunity to perform diagnostic whole-body ^{131}I scans without the associated morbidity of hypothyroidism. A randomized, prospective trial using 100 mCi of ^{131}I found comparable ablation rates with THW and rhTSH. The Food and Drug Administration consequently approved the use of rhTSH to stimulate thyrotropin (TSH) levels prior to remnant ablation with 100 mCi. Whether smaller amounts of ^{131}I will be associated with equivalent ablation rates with THW and rhTSH continues to spark research. The present study examines whether remnant ablation with 54 mCi (2 GBq) is comparable with THW and rhTSH.

METHODS All patients had papillary thyroid carcinoma (PTC) or minimally invasive follicular thyroid carcinoma (FTC), all of which were American Joint Committee on Cancer (AJCC; 5th edition) tumor–node–metastasis (TNM) stage <T1N0, a tumor 1 cm or smaller without lymph-node metastases. Cervical ultrasonography was performed in all patients to determine the absence of lymph-node metastases; all had either total thyroidectomy or near-total thyroidectomy, after which patients began levothyroxine (L-T_4) suppressive therapy. Patients with thyroglobulin antibodies were excluded from the study. All were treated with ^{131}I for 42 to 180 days after the initial surgery. Patients were randomly assigned to one of two pretreatment groups, both of which were placed on a low-iodine diet for 2 weeks prior to ^{131}I remnant ablation. A diagnostic ^{131}I whole-body scan using 0.5 mCi (18 MBq) was performed 24 hours prior to administration of the ablative dose. Radioiodine uptake was also measured to determine the extent of residual thyroid tissue and to assist in pretreatment staging. Four to 6 days after the ablative dose, a posttreatment whole-body scan was obtained.

Group A was prepared for ^{131}I remnant ablation by THW. This group comprised 21 patients (16 women [76%], 5 men [24%]) whose mean (±SD) age was 48±9.9 years. L-T_4 was stopped for 37 days; from the 3rd to the 22nd day after L-T_4 withdrawal, patients were treated with triiodothyronine (T_3). This group was treated with 54.6±5.9 mCi (2.02±.22 GBq)

Group B was prepared for ^{131}I ablation with two daily injections of rhTSH. This group comprised 21 patients (17 women [81%], 4 men [19%]) whose mean age was 46.2±12.3 years. In 18 patients (86%) the tumors were papillary or follicular variant PTC, and the others were follicular tumors. This group was prepared for ^{131}I therapy with two daily 0.9-mg injections of rhTSH and was treated with 53.2±4.9 mCi (1.97±0.18 MBq) of ^{131}I 24 hours after the last injection of rhTSH. For both groups, the success rate of remnant ablation was determined by a diagnostic whole-body scan performed 6 to 12 months after the treatment. Stimulation for this scan was performed with THW, and images were acquired 48 hours after the 5-mCi (185-MBq) dose of ^{131}I. Serum samples

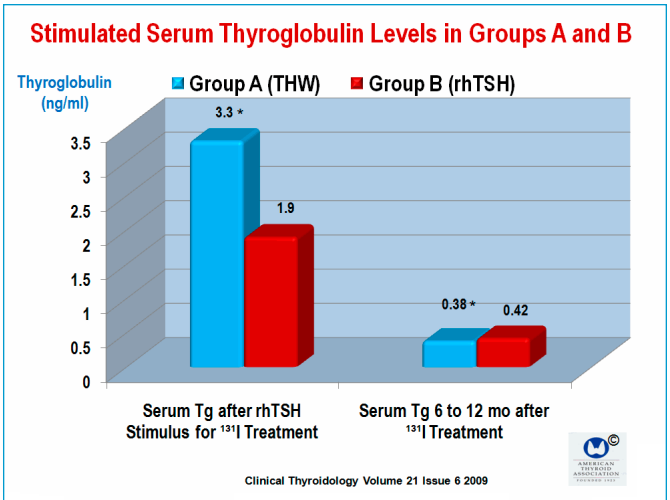

Figure 1. The THW or rhTSH-stimulated serum thyroglobulin (Tg) levels in groups A and B are shown at the time of initial treatment and 6 to 12 months after treatment. Patients in group B had Tg and TgAb levels assessed 3 days after the last rhTSH injection, and both groups had Tg levels measured 6 to 12 months after treatment. *P = not significant comparing group A with group B.

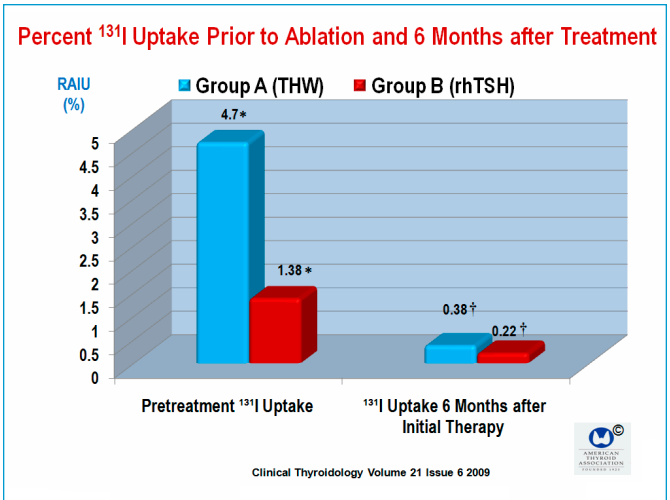

Figure 2. This figure shows the extent of radioiodine uptake (RAIU) prior to ablation and 6 months after initial treatment. Patients in group B received only one injection of rhTSH prior to this scan, which may have substantially lowered the pretreatment uptake. *P = 0.04. †P = not statistically significant, comparing group A with group B.

were obtained for TSH, free T_4 (FT_4), thyroglobulin (Tg), anti-Tg antibodies (TgAb), and urinary iodine excretion.

RESULTS There was no statistically significant difference in serum TSH levels at the time of treatment in groups A and B (77.9±17.1 vs. 91.00±9.8). Although the stimulated serum Tg levels at the time of treatment were slightly lower in the rhTSH group (1.9±2.15 ng/ml) than in the THW group (3.3±3.7 ng/ml), this difference was not statistically significant (Figure 1). The pretreatment ^{131}I uptake scan was significantly different between the two groups: the THW patients had a higher cervical ^{131}I uptake (4.7±4.55%) than the rhTSH group (1.38±1.14%) (P = 0.004) (Figure 2). However, patients in the rhTSH group had received only one injection at the time of the pretreatment scan, and therefore were not likely to have fully elevated TSH levels.

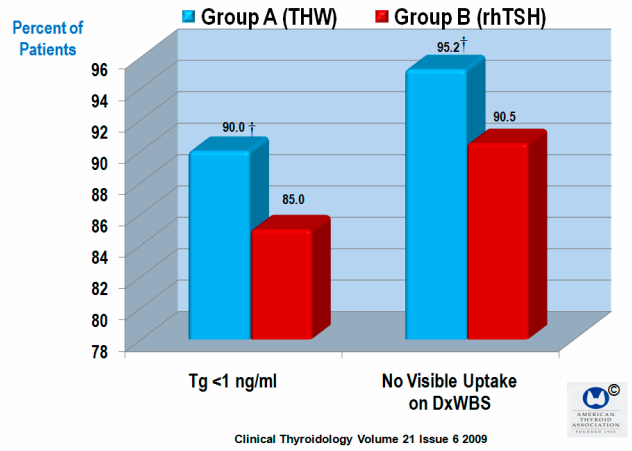

Figure 3. Outcomes of ^{131}I ablation with 54 mCi after patients were prepared with thyroid hormone withdrawal or rhTSH stimulation. DxWBS = diagnostic whole-body scan ; Tg = thyroglobulin; RAIU = visible ^{131}I uptake 6 to 12 months after remnant ablation. †P = not statistically significant, comparing group A with group B)

Evaluation for thyroid remnants was performed by ultrasonography; 5 patients in the THW group had a discernible remnant ^{131}I uptake as compared with 4 patients in the rhTSH group. In all cases the remnant volume was less than 1 ml. There was neither a significant difference in volumes of remnant tissue between the two groups nor an association between remnant sizes as measured by ultrasonography or ^{131}I uptake or ablation rate.

High rates of successful ablation were observed in both groups at the 6-month follow-up. There was no ^{131}I uptake in the diagnostic whole-body scan in 20 of 21 patients (95.2%) in group A and in 19 of 21 patients (90.5%) in the rhTSH group (group B) (P = not significant) (Figure 3). When analyzing the stimulated Tg as a measure of successful ablation, there were 20 evaluable patients, one of whom had undetectable levels at the time of treatment. Thus, Tg could not be used as an objective indication of complete ablation. Still, if a serum Tg <1 ng/ml were used to assess the efficacy of therapy, the rate of successful ablation was 90% in group A and 85% in group B (P = not significant). The three patients with mildly elevated stimulated Tg levels had values of 1.08, 1.12, and 1.37 ng/ml 6 to 12 months after treatment. In all patients in both groups, the Tg levels were undetectable while on L-T_4 suppressive therapy.

CONCLUSION In low-risk patients, preparation for ^{131}I ablation with 54 mCi has similar efficacy with THW or rhTSH stimulation based on comparable rates of negative diagnostic whole-body scans and stimulated Tg <1 ng/ml 6 to 12 months after therapy.

COMMENTARY

Whether to perform remnant ablation in patients with low-risk thyroid cancer is a controversial issue among endocrinologists (1,2). There are retrospective cohort studies that have found that its use significantly reduces the risk of recurrence and may improve mortality (3,4), whereas other studies (5,6) have shown no such benefit, especially when total thyroidectomy and prophylactic lymph-node total compartment dissection is performed (7). Postoperative surveillance is more sensitive, however, when remnant ablation is used. Patients who have not received radioiodine will continue to have measurable levels of Tg, making it impossible to differentiate benign from malignant sources. This is especially problematic, since both the American and European thyroid associations recommend that, in addition to negative clinical examination and imaging studies, serum Tg should be undetectable (<1 ng/ml) during TSH suppression and stimulation in the absence of interfering anti-Tg antibodies to reach a firm conclusion that a patient is free of disease (8,9). Thus, endocrinologists and patients often prefer to use radioiodine to simplify postoperative surveillance. Because thyroid hormone withdrawal is associated with significant morbidity, the possibility of substituting recombinant human TSH in preparation for remnant ablation has great attraction, particularly in low-risk patients. A recent multicenter trial showing comparable ablation rates with THW and rhTSH when using 100 mCi (10) has stimulated a number of other studies to investigate the use of rhTSH with small amounts of radioiodine in the range of 30 to 50 mCi.

Many clinicians would prefer to administer smaller amounts of ^{131}I to low-risk patients to minimize the associated risks of salivary-gland dysfunction and secondary malignancies. A study (11) that evaluated the efficacy of rhTSH and THW with 30 mCi for ablation showed that this dose is insufficient for a satisfactory ablation rate with rhTSH stimulation. In a subsequent study (12), the authors postulated that the reduced rates of successful ablation in the rhTSH group were the result of interference of excess iodine in the L-T_4 tablets. To test this theory in patients who received rhTSH, the authors of the study stopped L-T_4 the day prior to the first injection of rhTSH and restarted it the day after ^{131}I ablation. Ablation rates based on 12-month rhTSH-stimulated diagnostic whole-body scans and Tg levels were not significantly different between the patients initially stimulated with THW and those stimulated with rhTSH. These findings are encouraging concerning the possibility of using smaller amounts of ^{131}I with rhTSH stimulation, but further study of 30 mCi with rhTSH is needed to clarify these conflicting results. In the meantime, clinicians seeking to perform low-dose

remnant ablation may effectively use 50 mCi (13) to 54 mCi (the study under discussion) when stimulating with rhTSH.

More prospective studies are also needed to evaluate the efficacy of rhTSH-stimulated ablation of metastatic disease. However, there are several retrospective studies (14-16) that report successful remnant ablation in patients with lymph-node and distant metastases treated on a compassionate-use basis. rhTSH is not approved by the Food and Drug Administration for routine clinical treatment of distant metastases. Caution must be exercised when opting to treat patients with distant metastases—particularly those with tumor in enclosed spaces—because cases have been reported of sudden enlargement of neoplastic tissue after the stimulation with rhTSH, especially in elderly patients (17).

Long-term prospective data on the outcomes of patients treated with rhTSH-stimulated remnant ablation are likewise lacking. It is currently unknown whether the equivalence of remnant ablation using rhTSH and THW in preparation for ^{131}I therapy translates into comparable recurrence and mortality rates in the long term. A recent retrospective study (18) of patients treated with rhTSH-stimulated ablation compared to a historical control group that had THW found that the rates of persistent disease were lower in the rhTSH group, and that more patients had no clinical evidence of disease in the rhTSH group ($P = 0.02$). If these findings are reproducible in a prospective trial, the implications of administering rhTSH stimulation prior to remnant ablation may go beyond making patients feel better by not becoming hypothyroid.

Jennifer A. Sipos, MD

References

1. Hay ID. Management of patients with low-risk papillary thyroid carcinoma. Endocr Pract 2007;13:521-33.

2. Mazzaferri EL. Management of low risk differentiated thyroid cancer. Endocr Pract 2007;13:498-512.

3. DeGroot LJ, Kaplan EL, McCormick M, et al. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 1990;71:414-24.

4. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.

5. Hay ID, Thompson GB, Grant CS, et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. World J Surg 2002;26:879-85.

6. Hundahl SA, Fleming ID, Fremgen AM, et al. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the US, 1985-1995. Cancer 1998;83:2638-48.

7. Bonnet S, Hartl D, Leboulleux S, et al. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. J Clin Endocrinol Metab 2009;94:1162-7.

8. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109-42.

9. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803.

10. Pacini F, Ladenson PW, Schlumberger M, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. J Clin Endocrinol Metab 2006;91:926-32.

11. Pacini F, Molinaro E, Castagna MG, et al. Ablation of thyroid residues with 30 mCi (131)I: a comparison in thyroid cancer patients prepared with recombinant human TSH or thyroid hormone withdrawal. J Clin Endocrinol Metab 2002;87:4063-8.

12. Barbaro D, Boni G, Meucci G, et al. Radioiodine treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: effectiveness for postsurgical remnants ablation and possible role of iodine content in L-thyroxine in the outcome of ablation. J Clin Endocrinol Metab 2003;88:4110-5.

13. Pilli T, Brianzoni E, Capoccetti F, et al. A comparison of 1850 MBq (50 mCi) and 3700 MBq (100 mCi) 131-iodine administered doses for recombinant TSH-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. J Clin Endocrinol Metab 2007;92:3542-6.

14. Lippi F, Capezzone M, Angelini F, et al. Radioiodine treatment of metastatic differentiated thyroid cancer in patients on L-thyroxine, using recombinant human TSH. Eur J Endocrinol 2001;144:5-11.

15. Robbins RJ, Tuttle RM, Sonenberg M, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin. Thyroid 2001;11:865-9.

16. Robbins RJ, Driedger A, Magner J. Recombinant human thyrotropin-assisted radioiodine therapy for patients with metastatic thyroid cancer who could not elevate endogenous thyrotropin or be withdrawn from thyroxine. Thyroid 2006;16:1121-30.

17. Braga M, Ringel MD, Cooper DS. Sudden enlargement of local recurrent thyroid tumor after recombinant human TSH administration. J Clin Endocrinol Metab 2001;86:5148-51.

18. Tuttle RM, Brokhin M, Omry G, et al. Recombinant human TSH-assisted radioactive iodine remnant ablation achieves short-term clinical recurrence rates similar to those of traditional thyroid hormone withdrawal. J Nucl Med 2008;49:764-70.

www.thyroid.org/patients/ct/index.html