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RECOMBINANT THYROTROPIN FOR DETECTION OF RECURRENT THYROID CANCER

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ABSTRACT

Detection of recurrent thyroid cancer tumor requires TSH stimulation for radioiodine scanning and thyroglobulin (Tg) measurement. Temporary thyroid hormone withdrawal has previously been used, but causes hypothyroidism and, rarely, tumor progression.

Methods. The alternative of recombinant thyrotropin (rTSH) was assessed in two randomized clinical trials in which patients had ^{131}I and Tg testing twice: first after rTSH, and second after thyroid hormone withdrawal. Test results and quality of life were compared.

Results. In the first trial, among 62 of 127 patients with positive scans, rTSH was equivalent to withdrawal in 41, superior in 3, and inferior in 18 ($P < 0.05$), suggesting a lesser sensitivity of rTSH scans. In a second trial employing enhanced techniques, among 108 of 220 patients with positive scans, there was no difference in the number of superior rTSH and withdrawal scans. Furthermore, among all patients with withdrawal study evidence of residual thyroid tissue, 74% of all patients with residual thyroid tissue and 100% of patients with tumor metastases had rTSH-stimulated thyroglobulin values above 2 ng/mL. Naturally, patients experienced significantly more symptoms and diminished quality of life when hypothyroid than after rhTSH.

Conclusions. Combined rTSH-stimulated radioiodine and Tg testing is as sensitive as thyroid hormone withdrawal to detect recurrent thyroid cancer, and causes less morbidity.

INTRODUCTION

Primary treatment of well-differentiated thyroid cancers is highly effective. Surgical thyroidectomy is often followed by radioiodine ablation and always by lifelong TSH-suppressive thyroid hormone therapy. Despite the efficacy of primary treatment, patients have significant risk of recurrent disease that can occur even decades later (1,2). Al-

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though there are only 18,000 new thyroid cancer cases in the U.S. each year, almost 200,000 survivors require periodic monitoring for disease recurrence (3,4).

In addition to clinical assessment of thyroid cancer survivors, two diagnostic tests are highly accurate by virtue of certain tissue-specific characteristics of thyrocytes: 1) iodine concentration, which is detectable by radioiodine imaging (5), and thyroglobulin production (6,7). Both tests depend, however, on stimulation of thyroid cells by thyrotropin (thyroid-stimulating hormone, TSH) (5,8,9). Traditionally, testing has entailed temporary withdrawal of thyroid hormone therapy. While effective, this technique results in transient but severe hypothyroidism. Consequent TSH stimulation of residual thyroid cancer can also occasionally cause tumor progression with clinical consequences, particularly with paraspinal or intracranial metastases (10–12). Furthermore, some patients cannot surmount an endogenous TSH rise, including those with coincident pituitary disease (13), functioning metastases, and some elderly individuals.

To avoid these problems, several strategies have been tried. Bovine TSH was found effective (14,15), but had frequent side effects (16,17) and induced neutralizing antibodies (18). Human TSH, extracted from glands at autopsy, was also effective (19), but its supply was limited and there was risk of transmitting infection. A novel approach emerged with the cloning and sequencing of the human TSH beta subunit (20) gene and its stable co-transfection along with the common alpha subunit gene into a mammalian cell line (21–23). This produced an rTSH molecule with full TSH receptor binding and stimulatory activities in thyrocyte cultures and primate studies (24,25).

MATERIALS AND METHODS

Patients with differentiated epithelial thyroid cancers (i.e., papillary, follicular, and Hurthle cell cancers) for whom radioiodine scanning was clinically indicated gave written informed consent to undergo two whole body ^{131}I scans and quantitative uptakes (Figure 1): the first scan stimulated by rTSH while taking thyroid hormone (L-thyroxine, L-triiodothyronine, or both) in a dose sufficient to suppress the endogenous serum TSH concentrations to less than 0.5 mU/L; and the second scan after withdrawal of thyroid hormone therapy for at least two weeks and until the endogenous serum TSH was greater than 25 mU/L, a level traditionally considered adequate for imaging. rTSH (Thyrogen®, Genzyme Corp., Cambridge, MA) 0.9 mg intramuscularly was given daily for two days (protocols I and II, arm A) or every three

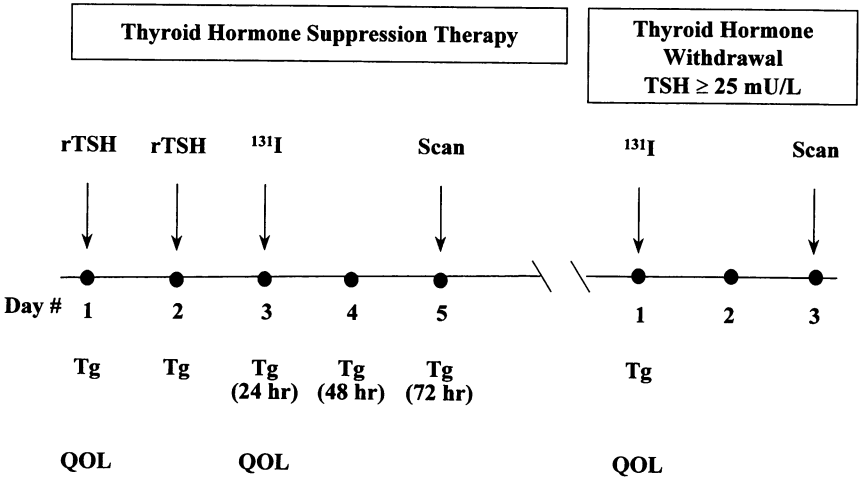

FIG. 1. General scheme of recombinant thyrotropin trials.

days for three doses (protocol II, arm B). Twenty-four hours after the final rTSH dose, patients received 2–4 mCi ^{131}I p.o., and 48 hours later, the first whole body scan was done. Thyroid hormone therapy was continued for at least two weeks, then discontinued to prepare patients for their second whole body ^{131}I scan, which was performed in an identical manner. Three reviewers blinded to the scan preparation method evaluated all scans, comparing the number and locations of foci between scan pairs to classify them as concordant or discordant. In discordant pairs, the scan with the greater number and/or more widespread distribution of foci was considered superior.

Serum thyroglobulin concentrations were assayed (Thyroglobulin RIA, Kronus, San Clemente, CA) 24, 48, and 72 hours after the final rTSH dose in 35 patients in protocol I and in all 220 patients in protocol II. Sera were screened for the presence of thyroglobulin autoantibodies (THYMUNE-T, Murex Diagnostics, Dartford, England), which interfere with accurate thyroglobulin quantitation; and those with interfering antibodies were excluded from further thyroglobulin-related analyses.

Patients' clinical statuses were assessed on study entry and before each scan, using the Billewicz scale (26), a disease-specific symptom survey for hypothyroidism, along with the short form Profile of Mood States (POMS) scale (27) in protocol I, and the SF-36 mental and physical component scales in protocol II.

Results are expressed as mean ± SD. The numbers of superior scans and detectable Tg findings with the two techniques were compared by

the McNemar Chi square test. Differences in symptoms, and POMS and SF-36 scores were analyzed by the Wilcoxon signed rank test.

RESULTS

Protocol I: Comparing Effectiveness of rTSH and Thyroid Hormone Withdrawal for 131-I Scanning and Impact on Clinical Status (28)

This trial addressed two questions: 1. Was TSH-stimulated 131-I scanning after rTSH stimulation as sensitive as that after withdrawal of thyroid hormone?; and 2) Would rTSH, in fact, avoid the symptoms and dysphoria associated with hypothyroidism? One hundred twenty-seven patients with previously treated thyroid cancer reflected the typical spectrum of tumor stages with their most recent previous radioiodine scan showing no uptake in three, thyroid bed activity only in 75, other cervical foci in 34, and intrathoracic and skeletal metastases in ten and five patients, respectively. Their mean serum TSH concentration before rTSH administration was suppressed, 0.2 ± 0.3 mU/L, and rose to 101 ± 60 and 132 ± 89 mU/L 24 hours after the first and second rTSH doses, respectively. Among all patients, 86% had a rTSH-stimulated scan that was concordant or superior to the withdrawal scan while 14% had superior withdrawal scans. However, 65 patients had concordant negative scans and only 62 patients had a positive radioiodine scan by one or both techniques. Forty-five of the scan-positive patients had only thyroid bed activity, while ten had cervical foci outside of the thyroid bed, five had thoracic activity, and two had distant bone or liver foci. The rTSH and withdrawal scans were concordant in 41 of these 62 patients (66%), superior after rTSH in three patients (6%), and superior after withdrawal in 18 patients (29%). The resulting tumor staging by the two techniques was equivalent in 40 patients (65%), including six of 11 with cervical activity, three of four with intrathoracic activity, and both patients with distant metastases.

There were more symptoms and signs of hypothyroidism after thyroid hormone withdrawal than after rTSH, which produced no more of these clinical findings than during the initial protocol evaluation. Weight gain, constipation, cold intolerance, slow movement, paresthesias, deafness, hoarseness, dry skin, and puffiness occurred much more often after thyroid hormone withdrawal. The Profile of Mood States revealed significantly more fatigue, depression, anger, tension, and confusion after withdrawal of thyroid hormone in comparison with rTSH. After rTSH, 16% of patient had nausea, which was generally

mild and short-lived. No patient in either trial developed detectable anti-TSH antibodies, including the patients who received multiple rTSH doses over several years.

Protocol II: Comparing the Sensitivities of TSH-stimulated Thyroglobulin Measurement and 131-I Scanning (29)

This trial addressed two questions: 1. Would the combination of TSH-stimulated serum thyroglobulin measurements and 131-I scans be equivalent after preparation with rTSH versus withdrawal of thyroid hormone?; and 2) Would more prolonged rTSH stimulation with three rTSH doses over ten days yield more sensitive scans in comparison the two-dose two-day regimen? Two hundred twenty patients were randomized to the previously employed two-dose two-day regimen or three doses of rTSH administered every 72 hours. Additional modifications in the scanning protocols were made to minimize "count poor" scans, and in the classification scheme for scan comparison to make it more clinically relevant.

Among the 220 patients, 108 had a positive radioiodine scan by one or both techniques: 48 and 60 in the two- and three-dose groups, respectively. Concordance of rTSH and withdrawal scans for all patients, patients with positive scans, and patients with a scan revealing metastatic disease are summarized in Table 1. Among patients with a positive scan, 100 of 108 had a rTSH scan that was equivalent or superior to the scan after thyroid hormone withdrawal. There were no significant differences in any group between the numbers of superior rTSH scans versus thyroid hormone withdrawal scans. Furthermore, there were no differences in the relative sensitivities of scans performed with the two- versus the three-dose rTSH regimens.

TABLE 1
rTSH and Withdrawal 131-I Scans in Thyroid Cancer Patients After the Two-Dose and Three-Dose rTSH Regimens

Group	Two-Dose Regimen			Three-Dose Regimen		
	Concordant	rTSH Superior	Withdrawal Superior	Concordant	rTSH Superior	Withdrawal Superior
All Patients	101 (89%)	9 (8%)	3 (3%)	94 (88%)	5 (5%)	8 (7%)
Scan-Positive Patients	36 (75%)	3 (5%)	9 (19%)	47 (78%)	5 (8%)	8 (13%)
Metastatic Disease*	14 (74%)	1 (5%)	4 (21%)	25 (83%)	1 (3%)	4 (13%)

* Patients with one or more foci of 131-I activity outside of the thyroid bed or a stimulated serum thyroglobulin greater than 10 ng/dL.

There was no significant difference for all comparisons between superior rTSH versus withdrawal scans, and between the two-dose and three-dose rTSH regimens.

Among all study patients with evidence of residual thyroid cancer or tissue based on scanning and thyroglobulin findings after thyroid hormone withdrawal (the "gold standard"), only 43% had a thyroglobulin level greater than 2 ng/mL when tested while remaining on TSH-suppressive thyroid hormone therapy (Figure 2). Even among patients with metastatic disease, the TSH-suppressed thyroglobulin was falsely negative in 23%. However, among all patients with positive withdrawal studies, 74% also had positive rTSH-stimulated testing. Finally, 100% of patients with metastases had rTSH-stimulated thyroglobulin values that were above the 2 ng/mL threshold.

Comparison of the SF-36 physical and mental component scores after rTSH administration and thyroid hormone withdrawal showed significantly higher physical component, but not mental component scores with rTSH (data not shown). Headache was the only adverse reaction observed more commonly after rTSH than during the baseline evaluation.

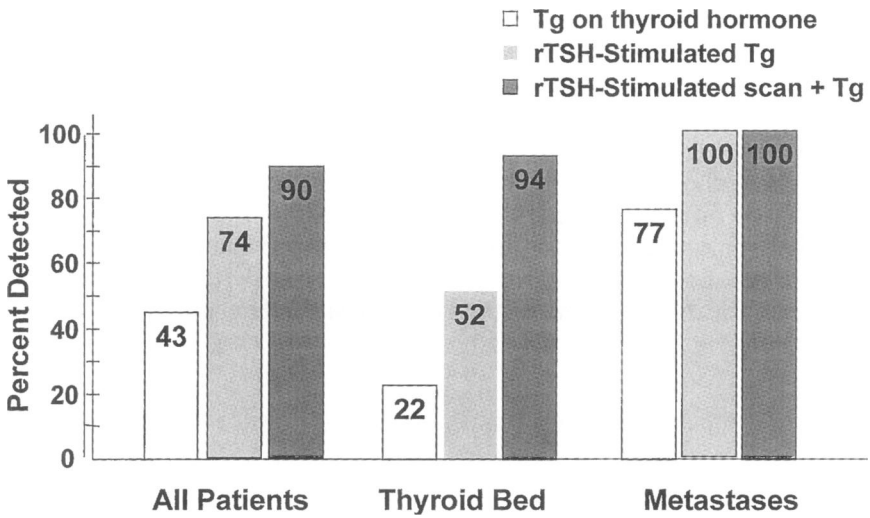

FIG. 2. Detection of thyroid cancer or tissue by thyroglobulin during TSH suppression, thyroglobulin after rTSH stimulation, and the combination of rTSH-stimulated thyroglobulin with 131-I scanning. Among all patients, those found to have only thyroid bed 131-I activity, and those with 131-I foci outside of the thyroid bed based on 131-I scanning and serum thyroglobulin testing (greater than 2 ng/mL) after the "gold standard" of thyroid hormone withdrawal, the percentages with a serum thyroglobulin level greater than 2 ng/mL when on thyroid hormone suppressive therapy, with a serum thyroglobulin level greater than 2 ng/mL after rTSH, and with either a serum thyroglobulin level greater than 2 ng/dL or a positive 131-I whole body scan after rTSH are shown. (Modified from Haugen BR, et al. J Clin Endocrinol Metab 1999;84:3877–3885.)

DISCUSSION

Two prospective randomized clinical trials have demonstrated the effectiveness and safety of rTSH for detection of residual or recurrent thyroid cancer after primary therapy (28,29). Avoidance of hypothyroidism makes rTSH-stimulated testing an attractive option for patients being monitored after all normal thyroid tissue has been ablated by total or near total thyroidectomy and radioiodine ablation. However, rTSH testing is usually inappropriate in patients who have had only partial thyroidectomy because residual normal thyroid tissue will yield "false-positive" 131-I scan and thyroglobulin. rTSH is also not required for patients who are already known to have residual thyroid cancer on the basis of other clinical, thyroglobulin, radioiodine scan, biopsy, or anatomic imaging findings.

Several factors should be considered in deciding when rTSH testing can replace thyroid hormone withdrawal during a thyroid cancer patient's postoperative follow-up. First, as noted above, all normal thyroid tissue should have been ablated. Second, the patient's initial tumor stage (30) and related pre-test probability of recurrent disease should be considered. For patients at low to moderate risk of tumor recurrence, rTSH-stimulated testing can be used for the first cycle of scanning and thyroglobulin measurement six to 12 months after postoperative 131-I ablation. For patients at high risk of harboring residual or recurrent thyroid cancer, it is prudent to obtain one cycle of negative 131-I scan and thyroglobulin testing after thyroid hormone withdrawal before employing rTSH-stimulated testing. This approach is advisable because of the possible greater sensitivity of 131-I whole body scans and the higher level of thyroglobulin stimulation after thyroid hormone withdrawal. Furthermore, rTSH is not currently FDA-approved to facilitate the subsequent 131-I therapy that is often indicated in these patients. Finally, when a patient has circulating anti-thyroglobulin antibodies limiting the accuracy of thyroglobulin assays, one cycle of withdrawal scanning is advisable since disease detection depends on 131-I scanning alone in this circumstance.

The frequency with which rTSH-stimulated testing should be employed is not yet well defined. In the past, clinicians have been restrained in recommending repeated testing by the morbidity of hypothyroidism. However, rTSH-mediated testing should not be overused simply because this can be avoided. As with any diagnostic test, clinicians must consider patients' pre-test probability of having recurrent thyroid cancer. This is very low for most thyroid cancer patients who are more than five years after apparently successful initial treatment, e.g., less than 1% per year. Testing patients who are at low risk of

disease recurrence too frequently will yield more false positive than true positive findings, which then engenders morbidity related to anxiety and further testing.

These trials have demonstrated the relative insensitivity of assaying the tumor marker thyroglobulin only during TSH suppressive thyroid hormone therapy. Among all patients with evidence of residual thyroid cancer or tissue by "gold standard" withdrawal testing, less than 50% had a serum thyroglobulin level above 2 ng/mL while on thyroid hormone. Even patients with metastatic disease had falsely negative thyroglobulin testing one-fourth of the time during thyroid hormone therapy. These realities underline the importance of periodic TSH-stimulated testing to detect recurrent disease early, when it can be treated more effectively.

Several important questions require further clinical investigation. Is rTSH-stimulated thyroglobulin measurement without radioiodine scanning appropriate for some patients? Does an undetectable TSH-stimulated thyroglobulin level permit certain declaration that a thyroid cancer patient is truly cured? And how effective is rTSH to facilitate radioiodine therapy? These and other studies will define optimal uses of this novel recombinant agent.

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DISCUSSION

Bransome, Aiken: Paul you are certainly one of the leaders in this area. As someone who is still following and trying to treat patients with differentiated thyroid cancer, I ask the inevitable; what about treatment protocols? Rumor has it that there is a study; could you give us a progress report?

Ladenson, Baltimore: As you point out, work is in progress to look at the efficacy of radioiodine therapy following recombinant TSH. There is evidence from nonrandomized controlled trials done at Memorial Sloan Kettering, that recombinant TSH is effective in abolishing thyroid bed remnants in previously operated thyroid cancer patients. Just this month, a prospective randomized multi-center trial in North America and Europe began looking at that question in a rigorous randomized prospective trial. So I hope we will have an answer in about two years. There has also been considerable anecdotal experience using recombinant TSH for the treatment of residual disease. Currently, there are small sets of circumstances where we consider this appropriate: patients who are unable to surmount an endogenous TSH response due to pituitary or hypothalamic disease; patients who have had severe medical or psychiatric complications previously of thyroid hormone withdrawal; and patients with disease adjacent to the central nervous system.

Griner, Washington, DC: I may have missed it, but did you indicate the gold standard for metastatic disease against which you measured the sensitivity of recombinant TSH?

Ladenson: Yes, the sensitivity data that I showed, the 90% standard all patients who by traditional withdrawal testing had any positive finding. A positive radioiodine scan, or a serum thyroglobulin concentration that stimulated to greater than 2 nanograms per ml.