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Expanding Indications for Recombinant Human TSH in Thyroid Cancer

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Introduction

On December 17, 2007, Genzyme Corporation (Cambridge, MA) announced that the U.S. Food and Drug Administration (FDA) had approved a supplemental indication for Thyrogen[®], its brand of recombinant human thyroid-stimulating hormone (rhTSH), to be used in combination with radioiodine to ablate, or destroy, the remaining thyroid tissue in patients who have had

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surgery for differentiated thyroid cancer. Although rhTSH was first approved for clinical use in the United States, most European and certain Asian and South American countries approved rhTSH for ablation of postsurgical thyroid remnants before the FDA action. In this article we review the timelines for rhTSH approval and present the views of experts from around the world regarding the expanding indications for rhTSH in thyroid cancer.* The commentary concludes with an editorial summary.

Timelines for rhTSH Approval†

On November 30, 1998, the FDA issued its first approval of rhTSH, as “an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with thyroid cancer” (1). In the original approval, provisions were made for thyroid cancer patients who were unable to mount an endogenous TSH response to hypothyroidism, such as those with pituitary failure. On September 3, 2000, rhTSH was approved in European Union countries‡ for preparation of Tg testing with or without radioiodine imaging for detection of thyroid remnants and well-differentiated thyroid cancer in adult postthyroidectomy patients maintained on hormone suppression therapy. Low-risk patients with well-differentiated thyroid carcinoma who have undetectable serum Tg levels on thyroid hormone suppression could be followed by assaying rhTSH-stimulated serum Tg levels. These indications were adopted in a similar time period by Liechtenstein, Norway, and Iceland, and similar indications were approved by Ukraine on May 17, 2004.

On February 23, 2005, rhTSH was approved in Europe for pretherapeutic stimulation and low-risk postthyroidectomy adult patients maintained on hormone suppression therapy for the ablation of thyroid remnant tissue in combination with 3.7 GBq (100 mCi) radioactive iodine (RAI). In Australia (2006), Malaysia (2007), Thailand (2007), and Singapore (2007), government agencies approved indications for rhTSH similar to that adapted by the FDA in 2007. As noted by Dr. Yamashita, rhTSH has not been approved for clinical use in Japan. Prior to the approval of rhTSH for remnant ablation in 2007, the FDA approved label changes on March 11, 2004, and January 1, 2006. These dealt with Thyrogen® Tg testing alone and in combination with radioiodine imaging in patients with metastatic disease and a Quality of Life statement, respectively. In 2006 rhTSH was approved for clinical use by many countries in South America (see below).

EXPERT COMMENTARY

Asia and Australia

Shunichi Yamashita—The recent approval of rhTSH as Thyrogen® (Genzyme Corporation, Cambridge, MA) by the U.S. FDA will have a valuable impact in the management of patients with well-differentiated thyroid cancer throughout the world. Until recently, management guidelines in the United States and Europe, as proposed by both the American Thyroid Association Guideline Taskforce (2) and the European Thyroid Cancer Taskforce (3), merely recommended Thyrogen® instead of thyroid hormone withdrawal for the detecting recurrence in patients with thyroid cancer. Now the FDA has expanded the use of Thyrogen® to preparation of patients for ablation of thyroid remnants by RAI. This was based on pivotal clinical studies. These studies suggested that the efficacy of Thyrogen® was similar

*“rhTSH” is used to refer to Thyrogen®, but TSH is a heterogeneous substance. It is likely that Thyrogen® is not completely identical to the multiple molecular forms of human TSH that occur *in vivo*. In the future other TSH-like or TSH antagonist agents synthesized by recombinant technology may become available for clinical use, and the term rhTSH will lose its specificity for Thyrogen®.

†http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist, Approval History, Letters, Reviews & Related Documents, accessed 4/2/2008.

‡Austria, Belgium, Bulgaria, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, and United Kingdom.

to thyroid hormone withdrawal in achieving ablation of thyroid remnants but had significantly less side effects than thyroid hormone withdrawal because patients did not need to discontinue their thyroid hormone replacement therapy.

In Japan, however, the official approval to use Thyrogen[®] even as a diagnostic means has not been issued yet, so that in this area it puts the country behind the United States and Europe. There is no gold-standard how to treat and follow patients with well-differentiated thyroid cancer, which generally has a good prognosis. It is essential to use rhTSH in accordance with standardized guidelines as this is likely to contribute to the care of patients where it is used, and provide experience and evidence to enhance patient care in the future. It is also important to overcome shortages of nuclear medicine facilities and have a better understanding of the risks and benefits of RAI therapy. In this sense more experience with Thyrogen[®] may be advantageous. Arguing for the approval of Thyrogen[®] is that it is one of the most effective approaches to facilitate the detection and staging of thyroid cancer and now appears to be an important tool in using RAI to ablate or destroy the remaining thyroid tissue in patients who have had their cancerous thyroids removed. It is my hope that the current FDA decision will promote clinical application of Thyrogen[®], both for follow-up diagnosis and to facilitate RAI therapy in Japan and other Asia-Oceania countries where Thyrogen[®] has not yet been received into medical practice.

Bruce G. Robinson—The use of rhTSH in the management of thyroid cancer has been one of the most significant therapeutic advances in thyroidology in the last decade. In many countries rhTSH is available for diagnostic use with the measurement of Tg and thyroid scanning in the follow-up of patients with differentiated thyroid cancer. The recent FDA approval of rhTSH for immediate postoperative ablation of remnant thyroid tissue will save patients from the need to be made hypothyroid in this period with its attendant morbidity and with arguable cost benefit. The FDA approval follows similar approvals in Australia (2006), Malaysia (2007), Thailand (2007), and Singapore (2007). Of course these approvals are not necessarily associated with patient access since funding for rhTSH is often restricted by the government and out of the reach of many deserving patients. In Australia for instance, the use of rhTSH for diagnostic purposes is restricted to patients who have had psychiatric problems or cardiac dysfunction with thyroid hormone withdrawal, and cost prevents many patients who do not meet these criteria from accessing the drug.

There seems little doubt that rhTSH is at least as effective as withdrawal of thyroxine (T4) in preparing for ablation of thyroid remnants and the morbidity is significantly lower. The FDA approval for this indication brings it into line with most developed countries. It is frustrating that an agent with such clear efficacy is not more widely available for all patients with thyroid cancer for diagnostic and therapeutic purposes. Provided that it is used by clinicians aware of the potential adverse effects in patients with cerebral or spinal metastases, it should be the definitive way to prepare patients for follow-up scans or treatment.

Europe

Christoph Reiners and Markus Luster—In patients with epithelial thyroid cancer, measurement of serum Tg for diagnostic purposes and administration of RAI for imaging and treatment usually require that serum TSH levels be elevated to at least 30 mU/L. As an alternate to thyroid hormone withdrawal, rhTSH can be administered to achieve serum TSH concentrations in the range of 100–150 mU/L 3–24 hours later (4). Approximately 1 day after they peak, serum TSH concentrations are usually still greater than 30 mU/L.** Since its

**The mean apparent elimination half-life of rhTSH is 25±10 hours.

introduction, the use of rhTSH has spread. It is estimated that thousands of doses of rhTSH have been administered to patients in the 7–8 years after its initial approval.

When considering the role of rhTSH as opposed to thyroid hormone withdrawal, quality of life is increasingly recognized as being of great importance. These patients usually have excellent survival but should adhere to a long-term monitoring program. An important difference between RAI imaging after thyroid hormone withdrawal and that after rhTSH administration is that patients are hypothyroid in the former state and euthyroid in the latter. In the euthyroid state there is a substantially higher renal clearance of radioiodine. Therefore, in a recent randomized trial (5) of rhTSH versus thyroid hormone withdrawal to ablate thyroid remnants with 3.7 GBq (100 mCi) ^{131}I RAI, there was a significantly lower radiation dose to the blood with the rhTSH method (0.11 ± 0.028 vs. 0.17 ± 0.061 mGy/MBq, $p < 0.0001$). A trade-off for the lower radiation exposure to extrathyroid tissues could well be a lower pool of circulating radioiodine available for targeting healthy or cancerous thyroid tissue, resulting in lower re-uptake in such tissue.

Numerous controlled studies in diagnostic and ablation settings have demonstrated rhTSH-aided scanning to have an equivalent and high sensitivity compared to thyroid hormone withdrawal. rhTSH-facilitated ablation of thyroid remnants also provides comparable results to ablation in the hypothyroid state. An advantage of rhTSH is that it allows more predictable timing and, often, more convenient scheduling of imaging or ablation procedures.

Although not approved as an indication, much experience has been accumulated using rhTSH as an adjunct to treatment of distant metastatic disease. No prospective, randomized trial of rhTSH-aided RAI treatment of thyroid cancer metastasis has been conducted, however. Assessment of the results for rhTSH for this purpose is complicated by the late- or end-stage status of most patients who have been treated to date and to the heterogeneity in patient characteristics and severity of underlying disease. A considerable drawback to using rhTSH is its high cost. Studies have suggested, however, that society and patients are repaid by improvement in productivity, fewer missed workdays, and maintenance of an acceptable quality of life.

Martin Schlumberger—We use rhTSH in low-risk thyroid cancer patients for radioiodine ablation of normal thyroid remnants after surgery, and for assessing cure during follow-up (2,3,6). The rationale for using rhTSH is based on prospective studies that demonstrated a similar efficacy of rhTSH and withdrawal, and that were performed either in patients following rhTSH and then following withdrawal (7) during follow-up or in randomized patients either to withdrawal or rhTSH administration for radioiodine ablation (8). The results of these studies were confirmed by many uncontrolled and mostly retrospective studies (6). In these patients, the advantages of using rhTSH instead of withdrawal are that rhTSH avoids hypothyroidism (and potential associated morbidity) and improves the quality of life (9); the use of rhTSH also reduces the societal cost of the procedure (10-12); finally, in case of administration of radioiodine, the renal clearance of radioiodine is faster, resulting for a similar administered activity in a lower dose by at least one third to extrathyroid tissues, and permitting a shorter stay in the radiation protection ward (6). Therefore, in our clinical practice, whenever stimulation by TSH should be performed in low-risk patients, we routinely use rhTSH instead of withdrawal.

There are still several questions concerning its use. The recommended activity to be administered for ablation of normal thyroid remnants was 3.7 GBq (100 mCi), but several non-randomized studies using 1.11 GBq (30 mCi) and a randomized study (13) comparing 1.85 and 3.7 GBq (50 and 100 mCi, respectively) have shown promising results. Prospective randomized studies on large numbers of patients are being performed comparing in terms of

efficacy and of medicoeconomic evaluation the stimulation method (either withdrawal or rhTSH) and the activity administered (30 versus 100 mCi). This should permit the definition of the optimal procedure.

The discovery of many thyroid cancers at an early stage and the improvement of initial treatment procedures have permitted a decrease in the rate of persistent or recurrent disease. It is important to perform restaging at around 9–12 months after initial treatment to assess if the patient is at very low risk of recurrence (high probability of cure). In low-risk patients who have previously undergone thyroidectomy and radioiodine ablation, restaging is achieved using rhTSH stimulation and neck ultrasound. If these are negative, follow-up consists of Tg determination on thyroxine and repeat ultrasound at regular intervals, and the daily dose of thyroxine can be reduced. In these patients, there is no need to repeat rhTSH stimulation test in the absence of suspicious abnormalities (14). Patients with low positive Tg at 9–12 months should undergo repeated rhTSH testing, while those with Tg above the institutional cut-off are treated. The newer “supersensitive” Tg assays may have a role in this setting, since it permits the discovery at an early stage of a higher percentage of persistent or recurrent disease during thyroxine treatment, but at the expense of a larger number of low but detectable serum Tg levels (15). Up to now, rhTSH stimulation provides the most reliable assessment of cure, and further studies are needed to assess the significance of these very low Tg levels.

In patients with known tumoral foci, the few available studies have shown that the radiation dose delivered to neoplastic foci following rhTSH is probably far lower than that delivered by a similar activity following withdrawal (16). Up to now, this is the rationale to restrict the routine use of rhTSH to low-risk patients. However, larger doses of RAI may be administered in these patients, and this is permitted by the higher renal clearance of radioiodine. A prospective study comparing dosimetry following rhTSH and then withdrawal is needed, before using rhTSH as a routine preparation for radioiodine treatment of neoplastic foci.

In conclusion, the availability of rhTSH has been a major progress in the management of thyroid cancer patients. rhTSH should be used routinely in low-risk patients whenever stimulation by TSH is required.

North America

David S. Cooper—Although studies published in 2001–2003 strongly suggested that Thyrogen[®] could be used for remnant ablation, it was not until the results of the international randomized controlled trial (8) became known that I began to use Thyrogen[®] routinely for this purpose in low-risk patients. And since it was approved for this indication in Europe in 2005, it was only a matter of time before the FDA would approve it for this indication here in the United States. The advantages of using Thyrogen[®] for remnant ablation include simplicity, the possibility of lower body radiation exposure (5), and maintenance of quality of life (9). The disadvantage is the cost, although some would argue that Thyrogen[®] is cost effective from a pharmaco-economic perspective (12). In my view, the admonition in the package insert that states “Due to the relatively small clinical experience with Thyrogen in remnant ablation, it is not possible to conclude whether long-term thyroid cancer outcomes would be equivalent after use of Thyrogen[®] or use of thyroid hormone withholding for TSH elevation prior to remnant ablation” is unduly conservative, since there is no logical reason that long-term outcomes would be any different with the two methods of remnant ablation.

For me, the major unanswered question is whether Thyrogen-mediated ablation can be performed with radio-iodine doses less than 3.7 GBq (100 mCi). Limited data suggest that this is the case (13), with 1.85 GBq (50 mCi) and 3.7 GBq (100 mCi) being equivalent in a small number of patients. On the other hand, ablation rates are lower with Thyrogen[®] using 1.11 GBq (30 mCi) (17). Therefore, whether the lower total body radiation dose observed with

Thyrogen[®] compensates for the need to use a larger dose of RAI than one might ordinarily use in some patients (i.e., 30 mCi) remains an important unanswered clinical question. Another issue for further study is whether Thyrogen[®] can be used for remnant ablation in high-risk patients.

Finally, the complexities of performing a diagnostic ¹²³I pretreatment scan when using Thyrogen[®] are daunting, since the scan needs to be inserted before the therapy dose in a very tight time window. Granted, many experts do not request pretreatment scans for their patients (2), but for those such as myself who have routinely done so for a variety of reasons, we have abandoned these in most cases because of the logistic difficulties, and simply administer a treatment dose. Another option, which would require Thyrogen[®] to be used on 2 successive weeks (1 week for diagnostic scanning and 1 week for treatment), is financially untenable for most patients. Thus, the approval of Thyrogen[®] will, almost certainly, lead to the demise of routine pretherapy scans.

I welcome the recent FDA approval of Thyrogen[®] for remnant ablation, and hope that future research will solve some of the important clinical questions that remain.

Ernest L. Mazzaferri—The introduction of recombinant human TSH- α (rhTSH) had an almost immediate impact on the management of differentiated thyroid carcinoma. The first two prospective clinical studies (7,18) of rhTSH demonstrated that administration of the drug was a safe and effective means of stimulating thyroidal radioiodine uptake and the release of Tg, while maintaining the patient in a euthyroid state and protecting the patient's quality of life (9). Patients shortly began asking their physicians for rhTSH-stimulated diagnostic whole-body ¹³¹I scanning rather than undergoing thyroid hormone withdrawal. The main impetus for this was that diagnostic whole-body ¹³¹I scanning had been for many years the principal means of identifying residual differentiated thyroid cancer. As a consequence, patients typically underwent yearly thyroid hormone withdrawals over an extended period, leaving them to endure recurrent symptoms of hypothyroidism. I vividly recall speaking to a large group of patients with thyroid cancer at the national Thyroid Cancer Survivors Association who not only expressed keen interest in rhTSH, but spoke disparagingly of their various bad experiences with thyroid hormone withdrawal. They knew without reading the medical literature that short-term hypothyroidism after levothyroxine withdrawal is associated with a significant decline in quality of life, and that hypothyroid symptoms were abolished by the continued administration of levothyroxine during rhTSH stimulation. Indeed, patients often became aware of this before their doctors recognized the major clinical impact that the drug would have on their practice.

By 1985 it had become apparent that serum Tg measurements performed after thyroid hormone withdrawal were more accurate in identifying residual tumor than Tg measured during levothyroxine suppression of TSH (19). The second prospective rhTSH study (7) found that rhTSH-stimulated serum Tg measurement was as accurate in identifying residual tumor as Tg measurements made during thyroid hormone withdrawal. A number of clinical studies subsequently found this to hold true in day-to-day practice (20-23). As a result, TSH-stimulated serum Tg measurement has become a key step in identifying patients with persistent tumor, which has been integrated into the American and European Thyroid Association guidelines for the management of differentiated thyroid carcinoma (2,3).

The recent approval of rhTSH preparation for ¹³¹I thyroid remnant ablation is most welcomed by patients, many of whom opted for this choice well before the drug had been approved for this indication by the FDA. From my stand-point, the most important finding of the initial international prospective randomized study by Pacini *et al.* (8), which compared thyroid hormone withdrawal with rhTSH for remnant ablation, was that rhTSH-stimulated ¹³¹I ablation was associated with 33% less total body radiation than thyroid hormone withdrawal. Probably

the two most worrisome problems about ^{131}I remnant ablation for patients and physicians alike are the adverse effects of the radioisotope on the oral cavity, parotid glands, and lachrymal ducts, and the possibility of developing radiation-induced secondary cancers. Both sets of complications are related to the cumulative radiation delivered by ^{131}I (24). Thus, anything that lowers total body irradiation is a welcome finding for patients, particularly in light of two recent studies (25,26) that found empirically administering ^{131}I in lieu of dosimetry is prone to underestimating total body radiation exposure. Even better news is the randomized prospective study by Pilli *et al.* (13) that found therapeutic ^{131}I activities of 1.85 GBq (50 mCi) and 3.7 GBq (100 mCi) are equally effective for thyroid remnant ablation in patients prepared with rhTSH, even in the presence of lymph node metastases.

The introduction of rhTSH into clinical practice has sparked research that no longer centers around the indication for total thyroidectomy in the management of thyroid cancer, something that was the main issue debated over decades. Now our debates center upon follow-up strategies and the role of more sensitive Tg assays in the follow-up management. All of this resulted from the introduction of a new drug, rhTSH, in a field that has had a paucity of new therapeutic drugs introduced over the past several decades.

Richard J. Robbins—Recombinant human TSH (rhTSH; Thyrogen[®]) was developed in the late 1980s as collaboration between academic physician-scientists and a young biotechnology company, Genzyme, Inc. It was the first recombinant human hormone to have a direct impact on the management of patients with thyroid disease. rhTSH was initially approved as an aid in surveillance testing for survivors of thyroid cancer. The FDA approval of rhTSH in November 1998 was based on two phase III trials, which demonstrated that the diagnostic accuracy of radioiodine and serum Tg testing was similar whether patients were prepared by thyroid hormone withdrawal or by rhTSH (7). Although the sensitivity of the whole-body radioiodine scans was somewhat lower following rhTSH preparation, the diagnostic accuracy of the rhTSH-stimulated serum Tg level was equal or better than preparation by hormone withdrawal.

While rhTSH was first developed as a diagnostic agent, it was clear to many thyroidologists that this hormone might also serve as an alternate means of increasing sodium-iodide symporter activity to aid in radioiodine remnant ablation. Perros (27) was the first to report that rhTSH could be used in the remnant ablation setting, while patients continued on thyroid hormone. The first series of successful rhTSH-assisted remnant ablation was reported in 2001 from the Memorial Sloan-Kettering Cancer Center (28). Many short retrospective reports have subsequently confirmed these findings. With the support of the Genzyme Corporation, a group of clinical investigators established and conducted an international randomized controlled trial comparing remnant ablation rates between patients prepared by thyroid hormone withdrawal or by rhTSH (8). In a study of 63 thyroid cancer patients, this team found that radioiodine remnant ablation rates, after administering 3.7 GBq (100 mCi), was comparable between the groups. Those who were prepared by rhTSH had a better quality of life and a longer effective half-time of radioiodine in the remnant, and they received less radiation to the blood (5,8). A subsequent report by Italian investigators (13) found similar high remnant ablation rates at 8 months using only 1.85 GBq (50 mCi). Nevertheless, until further studies determine the most effective amount of ^{131}I to be administered, 3.7 GBq (100 mCi) should be the standard.

The use of rhTSH to prepare patients for radioiodine remnant ablation was approved by the European Medicines Agency in 2005. The U.S. FDA requested a longer term clinical follow-up study to confirm the short-term imaging-based conclusion. According to the new FDA package insert, a 3.7-year follow-up study of patients from the randomized controlled study (8) found that 100% of evaluable patients in both groups had no visible uptake in the thyroid bed or total uptake of < 0.1%. No patient in either group had a definitive cancer recurrence.

Based on this finding, in December 2007, the FDA approved the use of rhTSH in the United States as an adjunctive treatment for radioiodine ablation of thyroid remnants in patients who have had total or near-total thyroidectomy for well-differentiated thyroid carcinoma without evidence of metastatic disease.

Unfortunately, the issue of the term “metastatic disease” has not been fully clarified in the new package insert. There is a very high incidence of loco-regional nodal metastases in patients with papillary thyroid carcinoma. These loco-regional nodal metastases are not considered distant metastases, and therefore rhTSH ablation could be utilized in those who have N1 disease. However, it seems clear, at present, that the FDA does not intend that Thyrogen[®] be used routinely to treat distant metastases. Unfortunately, it is very unlikely that any federal or industrial organization will support the cost of a randomized controlled trial of rhTSH-assisted radioiodine therapy of metastatic differentiated thyroid carcinoma. This is unfortunate, as many patients with metastatic disease postpone or avoid therapy with radioiodine because of the reluctance to become hypothyroid.

The FDA Indications and Usage statement includes this indication. It reads, “Thyrogen[®] treatment and testing may be used in patients who are either unable to mount an adequate endogenous TSH response to thyroid hormone withdrawal or in whom withdrawal is medically contra-indicated.” Although there are no prospective trials that have tested the safety or efficacy of rhTSH-assisted radioiodine treatment of metastatic disease, retrospective reports of compassionate use cohorts do exist. In aggregate, they suggest that those who cannot make TSH or who cannot medically tolerate hypothyroidism may benefit from rhTSH-assisted high-dose radioiodine therapy for distant metastases (29,30). The risks include expansion (sometimes acutely) of metastatic lesions, and hyperthyroidism in those with a significant thyroid remnant or T4-producing metastatic lesions. After many years of using both approaches, I am convinced that rhTSH-assisted radioiodine therapy of metastases, which takes up iodine, has been as successful as the same therapy in patients following thyroid hormone withdrawal. When considering high-dose radioiodine therapy for metastases, the use of blood and whole-body dosimetry should be strongly considered in order to avoid over- or under-treatment, especially in the very young or old (25).

Many times during my career, I have had thyroid cancer patients referred from other hospitals months after having had a thyroidectomy. They were told to stay off thyroid hormone replacement until they saw an endocrinologist. Some patients have arrived in an advanced state of hypothyroidism because their follow-up was not arranged in a timely manner. With this expanded indication for rhTSH, it may become routine for patients to be placed on thyroid hormone replacement at the time of surgery, and then undergo remnant ablation, if indicated, without ever having to be hypothyroid. The cost-benefit analysis and the improved quality of life that these patients gain by not becoming hypothyroid appears to outweigh the expense of the Thyrogen[®] medication (6,10).

In summary, thyroidologists should applaud the FDA for expanding the indications for the use of rhTSH, and we should thank the Genzyme Corporation for supporting the long-term studies that were needed to assure the FDA that this approach was safe and effective.

South America

Rui M.B. Maciel and Rosa P.M. Biscolla—Following the European approval for the preparation of patients for thyroid ablation with rhTSH and 3.7 GBq (100 mCi) ¹³¹I on levothyroxine (L-T4) in 2005 (European Medicines Agency 2005, Decision C478 of 23=02=2005), agencies in charge of drug regulations of several Latin American countries also have approved the use of rhTSH to prepare patients to destroy thyroid remnants after surgery. Thus, ¹³¹I ablation using rhTSH was approved in several countries as Argentina, Brazil, Chile,

Colombia, Mexico, and Peru (Brazilian Medicines Agency (ANVISA), Decision 4034 of 08=12=2006). In Colombia rhTSH was approved to prepare only low-risk patients for thyroid ablation and a minimum of 3.7 GBq (100 mCi) ^{131}I therapeutic activity must be used, but in Brazil, Argentina, and Mexico, however, physicians can use any activity of ^{131}I and the use of rhTSH on L-T4 is not restricted for low-risk patients.

Although in Brazil we do not have any recommendation about which ^{131}I activity is better and which type of patients should be prepared with rhTSH, we believe, at this time, that we should use rhTSH only for low-risk patients on L-T4 (T1-T2, N1 and M0, patient age < 45 years) and to employ a minimum dose of 3.7 GBq (100 mCi) ^{131}I therapeutic activity (31).

Several aspects should be addressed in future studies to delineate the best strategy for the use of rhTSH to facilitate the postsurgical thyroid ablation, since recent reports do not clearly define the best effective activity of ^{131}I , the time and utility for low-iodine diet, the utility of a short L-T4 stoppage, the use of levo-triiodothyronine (L-T3) instead of L-T4, and the appropriate dose of rhTSH (5,13,32).

Geraldo Medeiros-Neto—There is no consensus that thyroid remnant ablation preceded by rhTSH is indicated for low-risk patients after total thyroidectomy. In a recent publication (31) thyroid ablation was recommended for many patients after total thyroidectomy for thyroid cancer but not for those whose risk was low. My informal consultation with several prominent clinical endocrinologists in Brazil, however, indicated that in almost all patients most would recommend an out-patient dose of RAI (1.11 GBq, 30 mCi) preceded by rhTSH. The rationale is to have a better imaging of residual thyroid tissue by whole-body scan during follow-up and, more importantly, to be able to use serum Tg as a marker of active disease. In other countries like Chile, thyroid ablation is favored for low- and high-risk patients with thyroid cancer. rhTSH is seldom used for this purpose, however, as it only became available in 2007 and is still quite expensive. In Argentina, rhTSH preceding ablation with RAI is generally used for patients considered to be at high risk. Low-risk patients are treated only with total thyroidectomy. A recent paper from Brazil (33) recommended a conservative approach with no postsurgical RAI ablation for patients with small, apparently single, thyroid cancers. Patients with thyroid cancer who have been operated on by surgeons without training in thyroid surgery often have large thyroid remnants. These patients, when referred to a University Hospital, are often treated with RAI ablation preceded by rhTSH.

The cost of rhTSH is an important consideration for patients who are candidates for its use in preparing them for RAI ablation. In most countries of Latin America, for the general population, either there is no refund from the National Health Plan or this modality of treatment is only available at Public and University Hospitals. Patients with private health insurance are usually reimbursed up to 70% for the cost of rhTSH. If the health insurance company refuses to reimburse the cost of rhTSH, most courts will decide in favor of the patient. In fact, in Brazil, almost all health insurance companies are paying the total cost because of previous court decisions. Moreover, free assistance regarding the patient's legal rights is now provided by a number of private institutions.

In conclusion, there is a strong tendency in both low- and high-risk patients, for clinical endocrinologists in Latin America to use ablation with 1.11 GBq (30 mCi) or higher doses of RAI in cancer patients after thyroid surgery and to employ Thyrogen[®] to prepare patients for ablation. The major restriction to this is that patients may not be able to pay for the treatment and lack private insurance. In this case they will need to wait for many months to obtain the treatment in a public or university hospital.

Editorial and Summary^{‡‡}

There is general agreement among the experts featured here that rhTSH is an effective method to prepare patients with low-risk thyroid cancer for postsurgical ablation of thyroid remnants with RAI and that the 2007 decision of the FDA to add this as an indication will benefit patients in the United States. Other areas of unanimity include the impression that rhTSH administration provides better quality of life than thyroid hormone withdrawal by avoiding hypothyroidism. Expense was recognized as a major drawback, particularly in countries where there is little insurance coverage or rhTSH is not covered by the prevalent insurance programs. Counterbalancing this was the belief that the expense of rhTSH is made up for by better productivity than occurs during hypothyroidism when thyroid hormone is stopped.

We agree with Dr. Robbins' observation that some patients who are scheduled for remnant ablation after thyroid hormone withdrawal have an unanticipated delay in their treatment, resulting in severe hypothyroidism. Sometimes this is due to noncompliance on the part of the patient, sometimes to scheduling conflicts, and sometimes to the physician's efforts to reach an acceptable TSH level before administering RAI. The frequency that this occurs is difficult to ascertain as instances of inappropriately delayed RAI treatment are not likely to be reported. Use of rhTSH, however, avoids this problem.

There were few overt disagreements among commentators, but there were gray areas and controversial issues that surfaced. One concerns the ablative dose of radioiodine required for remnant ablation after rhTSH. Some believe we should use the 3.7 GBq (100 mCi) dose used in the randomized study by Pacini *et al.* (8). Others feel that the recent study of Pilli *et al.* (13) supports the use of doses as low as 1.85 GBq (50 mCi), and still others believe that 1.11 GBq (30 mCi) is sufficient.

Although not discussed in some of the commentaries, there is ongoing debate of the utility of pretreatment diagnostic radioiodine scans, usually with ¹²³I, in low-risk patients. Using the standard two-dose rhTSH protocol does not allow for diagnostic whole-body scans and conventional timing of treatment. Some experts are abandoning the diagnostic scan, some avoid rhTSH so they can do both the diagnostic scan and treatment, and others are getting creative by giving rhTSH on day 1 and 2, a ¹²³I dose on the afternoon of day 2, a ¹²³I whole-body scan on the morning of day 3, and ¹³¹I treatment on the afternoon of day 3. In this scenario, however, the decision to treat is based on whether or not there are residual postthyroidectomy remnants or for dose adjustment in the presence of distant metastatic disease. As emphasized by several of the commentators, rhTSH is not currently approved by the FDA to prepare patients with metastatic disease for RAI treatment. Nonetheless, it is important to develop protocols for rhTSH-facilitated ablation that incorporates a pretreatment whole-body scan.

We are in general agreement with the opinions of the commentators that rhTSH is definitely valuable in preserving quality of life as opposed to thyroid hormone withdrawal. This is certainly of great personal value to patients and their families. It is difficult to calculate the exact economic impact on the individual and society, although a few studies have examined this effect (12,34). We also agree with the commentaries that whole-body irradiation is reduced by using rhTSH rather than thyroid hormone withdrawal, and this should be a factor in reducing the risk of a second cancer.

One of the most controversial areas, however, concerns which patients need radioiodine remnant ablation. The decision for use of radioiodine for remnant ablation has been based on the impact of this treatment on overall survival, disease-free survival, and ability to monitor patient with sensitive testing (neck ultrasound and sensitive serum Tg testing). Most experts

^{‡‡}Editors Haugen, Emerson, and Pacini.

agree that patients with stage III and VI (AJCC, TNM) disease benefit from radioiodine remnant ablation, which is supported by the evidence (35). Evidence for effectiveness of remnant ablation in low-risk stage I patients, however, is lacking. A therapy-directed approach has been proposed, which divides patients into three basic risk categories when considering radioiodine therapy. These are very low risk, such as a solitary tumor less than 1–1.5 cm; high risk, such as a tumor with extrathyroid extension and/or distant metastatic disease; and low to moderate risk, which is intermediate (35). Patients with very low-risk disease are unlikely to benefit from radioiodine remnant ablation, and many patients with low-to-moderate risk disease may not benefit, especially younger patients with smaller tumors (<2 cm) and no worrisome features (extensive lymph node [LN] involvement and aggressive histology). Future research should focus on who would benefit, based on disease-free survival, from radioiodine remnant ablation.

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