INVITED COMMENTARY

Coming of Age: Recombinant Human Thyroid-Stimulating Hormone as a Preparation for ^{131}I Therapy in Thyroid Cancer

Recombinant human thyroid-stimulating hormone (rhTSH) was approved for diagnostic testing by the U.S. Food and Drug Administration in November 1998. It has subsequently been approved in Europe and Australia and is available in many other countries on a restricted basis. Approval was based on its ability to stimulate the uptake of radioiodine into thyroid remnants and metastases of thyroid cancer, as well as its ability to stimulate normal or neoplastic thyroid cells to produce thyroglobulin. In fact, the ability of rhTSH to stimulate the production of thyroglobulin, as judged by a rise in serum thyroglobulin above 2 ng/mL, is now recognized to be the most sensitive marker of residual thyroid cancer.

The ability to visualize a thyroid remnant or a metastatic deposit of thyroid cancer cells with radioiodine depends on several factors. The first is the number of cells present in a single focus, that is, a critical mass. Another is the iodine transporting capacity, which depends largely on the sodium iodide symporter (NIS) activity. A third factor is the trapping ability of the thyroid cells, which is related to the organification of iodine by the cells that accumulate it. Finally, there are incompletely defined mechanisms (e.g., pendrin) that export or clear iodine from the cells. If there are too few cells or if they cannot sufficiently accumulate or retain the radioiodine, they will not be visible by standard imaging techniques.

Haugen et al. (*1*) and our group (*2*) have independently reported, in large controlled series, that the sensitivity and specificity of whole-body radioiodine imaging is comparable whether patients are prepared by thyroid hormone withdrawal or by rhTSH. However, there is growing awareness of the poor sensitivity that a diagnostic whole-body scan has for detecting small volumes of residual disease (*3–5*).

The ability of thyroid-stimulating hormone (TSH) to increase the expression of NIS and to enhance radioiodine uptake raises the question of whether this new agent could also substitute for thyroid hormone withdrawal as a preparation for radioiodine therapy. TSH is also known to stimulate iodine efflux mechanisms in thyroid cells; however, the time course of this effect may be different from that of the effects on uptake (*6*). In general, radioiodine therapy is performed with ^{131}I and either is designed to ablate a thyroid remnant after a total thyroidectomy or is aimed at destroying metastatic thyroid cancer deposits that have demonstrated some radioiodine avidity.

The therapeutic setting raises new and important issues regarding rhTSH that were not addressed in the original diagnostic paradigms. The first issue is total-body radiation exposure after therapeutic amounts of ^{131}I. Temporary or permanent damage to bone marrow, bladder, oral mucosa, taste buds, salivary glands, gastric mucosa, and gonads has been reported after administration of ^{131}I (*7*). Side effects related to ^{131}I in the hypothyroid state occur in as many as 50% of the patients who receive large amounts of ^{131}I (*8*). Furthermore, it is well established that renal blood flow and glomerular filtration are reduced in hypothyroidism (*9,10*). Because iodine is principally cleared by the kidney, the prolonged retention of ^{131}I in the hypothyroid state would be expected to increase radiation to many tissues. The hypothyroid state, however, is a convenient and inexpensive means to raise endogenous pituitary production of TSH, which in turn would stimulate NIS activity in remnants or metastases.

On the other hand, if patients were prepared for therapy in the euthyroid state, with rhTSH, rather than in the hypothyroid state, the renal clearance of iodine should remain intact, leading to more rapid clearance of ^{131}I from the blood, with lower radiation of blood and tissues. This hypothesis has been tested and confirmed to be correct by several groups (*11,12*). This has led some investigators to administer therapeutic activities that are significantly higher than they would use in the hypothyroid state (*13,14*).

A second issue to consider is the "dwell time," or the duration of ^{131}I occupancy within the thyroid (normal or neoplastic) cells. If the radioiodine also clears from the target tissue more quickly in the euthyroid state, with rhTSH, than in the hypothyroid state, then rhTSH preparation may have little therapeutic advantage. In theory, a longer dwell time will result in a higher death rate of the target cells. The trapping of radioiodine into thyroid proteins or lipids would significantly increase the dwell time of the radioisotope, with tissue-specific damage. The frequently diminished expression of NIS, thyroperoxidase, and thy-

Received Mar. 13, 2003; revision accepted Mar. 24, 2003.

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roglobulin production in malignant thyroid tissues (*15*) could result in much shorter dwell times for radioiodine in neoplastic thyroid cells. Similarly, the responses of membrane proteins or mechanisms that export iodine from the cell to a rapid TSH exposure are not well characterized (*16,17*).

A third issue to be considered between a hypothyroid preparation and an rhTSH preparation is the rapid drop in serum TSH that occurs with the latter method. TSH increases both the influx and the efflux of iodine from normal thyroid tissue. A rapid increase in serum TSH followed by a rapid decrease, as occurs with rhTSH injections, may activate influx and efflux mechanisms differentially. If the ratio of influx to efflux is increased, a longer dwell time of radioiodine within neoplastic thyroid cells may result. This central question needs careful analysis if we are to fully evaluate the potential of rhTSH preparation. Many other issues will certainly appear as more experience is gained with the rhTSH method of preparation for radioiodine therapy.

In this issue of *The Journal of Nuclear Medicine*, Menzel et al. (*18*) have contributed new information to our collective experience of using rhTSH as a possible preparation for ^{131}I therapy. They retrospectively reviewed the whole-body clearance rate of ^{131}I in 227 thyroid cancer survivors treated at their medical center. Hypothyroid preparation was used in 163, and rhTSH preparation was used in 64. Using a sodium iodide probe, Menzel et al. obtained daily whole-body measurements from 2 to 6 d after the therapeutic administration of ^{131}I. They found that the mean effective half-life was approximately 26% longer in patients prepared by thyroid hormone withdrawal. For an identical administered activity, therefore, there would be more total-body radiation for those who were hypothyroid. When those patients who had no evidence of residual disease or remnants were eliminated, this significant difference persisted. This 26% slower clearance was slightly less than other preliminary studies had predicted but was qualitatively similar.

This is the largest study to date to confirm the presumption that the hypothyroid state results in prolonged whole-body exposure to a therapeutic administration of ^{131}I. This is in agreement with preliminary whole-body clearance data from a collaborative dosimetry study (*19*). What the study does not tell us is equally important. Did the prolonged clearance of ^{131}I result in more, less, or similar radiation to the remnant or to metastatic lesions? In a small group of patients, Luster et al. found that ^{131}I resided longer in thyroid remnants when the patients were prepared for therapy with rhTSH rather than with thyroid hormone withdrawal (*19*). Does the rhTSH preparation alter the dwell time of ^{131}I within the metastatic lesion? A recent publication by de Keizer et al. suggests that rhTSH preparation results in a median effective half-life in metastatic lesions of 2.7 d (*20*), which is similar to that reported by Maxon et al. (*21*) for hypothyroid patients. Was the outcome of the 2 preparations similar in terms of partial or complete destruction of the target tissue? Preliminary results from our center suggest that this may be the case for thyroid remnants (*22*) and for metastatic lesions (*23*). These important issues will need to be thoroughly addressed before we can feel assured that preparation by rhTSH is comparable to preparation by thyroid hormone withdrawal. If the outcomes are similar, then the reduced whole-body radiation that occurs in the euthyroid state might be sufficient, ipso facto, to recommend rhTSH preparation. Similarly, the avoidance of the physical and neuropsychologic sequelae of hypothyroidism is a strong argument for rhTSH preparation if it is at least as effective as hypothyroid preparation. On the other hand, the only clinically available formulation of rhTSH is a relatively expensive one-time cost. What is difficult to quantify, although it is certainly present, is the "cost" of being hypothyroid, in terms of interruption of work or school time (*24*). In conclusion, the study of Menzel et al. (*18*) confirms the physiologic hypothesis and other preliminary data that, compared with the euthyroid state after rhTSH, the hypothyroid state significantly increases the whole-body radiation received for a given administered activity of ^{131}I.

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