Management of Differentiated Thyroid Carcinoma with Radioiodine and Recombinant Human TSH

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Abstract. Recombinant human TSH (rhTSH) brought revolutionary change in the management of patients with differentiated thyroid cancer since it was first approved for clinical use in the United States and Europe. Follow-up management of differentiated thyroid cancer is based on the detection of recurrent or residual cancer, traditionally achieved by measurement of serum thyroglobulin level and various imaging techniques including 131I whole body scan. Previously, TSH stimulation was achieved only by induction of hypothyroidism following withdrawal of thyroid hormone. However, hypothyroidism is uncomfortable and is association with a reduction in quality of life. RhTSH can provide elevated TSH without making patients hypothyroid. In the United States and Europe, rhTSH is approved for use only in monitoring of differentiated thyroid cancer. In this article, we reviewed the role of rhTSH in the diagnosis and management of differentiated thyroid cancer.

Key words: Differentiated thyroid cancer, Recombinant human TSH, Thyroglobulin, Whole body 131I scan

IT is well known that the prognosis of papillary and follicular (differentiated) thyroid carcinoma is generally good. However, recurrence is not uncommon, affecting 20% of the patients with the disease [1]. The standard management of patients with well differentiated thyroid carcinoma in the United States and European countries is repeated radioiodine therapy until the serum TSH-stimulated thyroglobulin (Tg) decreases to a sufficiently low level, followed by total thyroidectomy [2, 3]. Because radioiodine plays an important role in the management of well differentiated thyroid carcinoma in these countries, use of recombinant human TSH (rhTSH) has become popular. The principal clinical utility of rhTSH has been for diagnostic monitoring in patients with differentiated thyroid cancer. Emerging uses for rhTSH include thyroid remnant ablation, treatment of metastatic thyroid cancer, treatment of nodular goiter and TSH stimulation PET scanning.

Japanese endocrinologists and endocrine surgeons, on the other hand, have been using a different strategy to manage well differentiated thyroid cancer [4]. An analysis of questionnaire survey of members of the Japanese Society of Thyroid Surgery in 2004 revealed that about 80% of the responders choose less than total thyroidectomy for patients with papillary thyroid carcinoma 3 cm in diameter. Because of the strict safety rules regarding the use of radioiodine in Japan, the reluctance to use postoperative radioiodine ablation seems to have caused endocrine surgeons to resign themselves to performing less than total thyroidectomy in order to avoid surgical complications as much as possible.

In this paper, we review the utility of rhTSH for the diagnosis and management of patients with well differentiated thyroid carcinoma.

History

The glycoprotein hormones TSH, FSH, and LH consist of two distinct subunits, an alpha subunit and a
beta subunit. All three hormones share a common alpha subunit, and their specificity is governed by their unique beta subunits. Two separate groups cloned the human beta subunit in 1988 [5, 6]. The dimeric form of rhTSH was generated in vitro by transfecting both the TSH alpha and beta subunits into various types of cells, and rhTSH was reported to stimulate cAMP generation, Tg production, and proliferation by thyroid cells [7, 8]. In 1997, a study designed to examine the effects of rhTSH on the function of the normal human thyroid demonstrated that the serum triiodothyronine and thyroxine levels both rose rapidly within several hours after intramuscular injection [9], and in 2001 rhTSH was demonstrated to increase thyroidal radioiodine uptake in healthy subjects [10].

Clinical utility of rhTSH

Approval to use rhTSH in the United States was granted by the Food and Drug Administration in 1998, and approval to use it in Europe was granted by the European Agency for the Evaluation of Medicinal Products in 2001. The clinical use of rhTSH has mainly been approved for the diagnostic monitoring of patients with differentiated thyroid cancer. Many potential uses of rhTSH have been proposed and reported (Table 1), and this review will explore its diagnostic utility for monitoring patients with differentiated thyroid cancer, an approved use in the United States and Europe.

The British Thyroid Association [2] and the American Thyroid Association [3] have recently published guidelines for the management of differentiated thyroid cancer. As described above, patients with differentiated thyroid carcinoma are treated by radioiodine ablation followed by total or near-total thyroidectomy, a strategy that has been reported to decrease recurrence and mortality. The standard method of follow-up and monitoring of patients with differentiated thyroid carcinoma is by Tg measurements both on TSH suppression therapy and after TSH stimulation, and by diagnostic whole body 131I scans (DxWBS). TSH stimulation used to be performed only by withdrawal of thyroid hormone. However, induction of hypothyroidism often reduces patient’s quality of life, and elevated TSH levels persist for weeks and may induce tumor growth. The development and clinical application of rhTSH has made it possible to raise serum TSH level without inducing hypothyroidism.

1. Diagnostic use of rhTSH in the evaluation of disease status: comparison between DxWBS following rhTSH stimulation and following thyroid hormone withdrawal

There have been three prospective studies and one retrospective study that examined the utility of rhTSH in thyroid cancer patients monitoring. The first study was a prospective, non-randomized Phase I/II trial of 19 patients with well differentiated thyroid carcinoma in 1994 [11]. After thyroidectomy, the patients were treated with T3 to suppress the endogenous TSH level. No patients had undergone ablative therapy with 131I. As thyroid hormone therapy was continued, 7 different regimens of various doses of rhTSH (10–40 U intramuscularly) were administered on 1–3 consecutive days. Twenty-four hours after the final rhTSH injection, 1–2 mCi 131I were administered, and a DxWBS was performed 48 h later. Immediately after the scan, T3 was withdrawn, and standard hypothyroid testing was performed (TH withdrawn). TSH, Tg, and 131I uptake all increased after administration of the rhTSH preparation. Peak serum TSH levels (mean) after a single dose of 10, 20, and 30 U were 127, 309, and 510 mU/L, respectively, and occurred 2–8 h after the injection. Dx WBS was compared between the both preparations, and in 12 (63%) of the 19 patients the scans were concordant. The scans of 6 patients were not identical. Three (50%) had better scans, visualized only after rhTSH and 3 (50%) had better scans after TH withdrawn.

This Phase I/II study was followed by two Phase III studies. In the first Phase III trial [12], in 1997, 127
patients with differentiated thyroid carcinoma were enrolled in this prospective, multicenter study. Two DxWBSs were obtained in each patient, the first scan after administration of rhTSH given 0.9 mg once a day for two days while the patients continued on thyroid hormone therapy, and the second after withdrawal of thyroid hormone therapy. Each patient was given 2 to 4 mCi of 131I for each scan, and a Dx WBS was obtained 48 h later. The Dx WBS following TH withdrawal was compared to the scan after administration of rhTSH. Both scans were negative in 65 patients (51%), and the other 62 patients had a positive scan by one or both techniques. The Dx WBS findings were concordant by both techniques in 106 (83.5%) of the patients. The scans were equivalent in 41 of the 62 patients who had at least one positive scan. The scan after administration of rhTSH was positive in 3 patients (5%), and the scan after withdrawal of thyroid hormone was positive in 18 (29%). The other Phase III trial was published in 1999 [13]. In that study was conducted on 220 patients with differentiated thyroid cancer, and two different rhTSH protocols were compared: 0.9 mg rhTSH on 2 consecutive days (Arm I) vs. 0.9 mg on days 1, 4 and 5 (Arm II). All scans were obtained 48 h after 4 mCi (148 MBq) dose of 131I (72 hours following the final dose of rhTSH). The second scan in patients in both Arms was obtained at least 2 weeks after withdrawal of thyroid hormone. The Dx WBS was compared between both preparations, and in 195 (89%) of the 220 patients the scans were concordant, and in 25 they were discordant. The scan after administration of rhTSH was positive in 8 patients (4%), and the scan after withdrawal of thyroid hormone was positive in 17 (8%). The percentages were almost the same in Arm I and Arm II. The scans were equivalent in 83 (77%) of the 108 patients who had at least one positive scan. In 8 patients (7%), the scan after administration of rhTSH was positive, and the scan after thyroid hormone withdrawal was positive in 17 (16%). The percentages were almost the same in Arm I and Arm II. This study also measured the Tg level following rhTSH administration or thyroid hormone withdrawal. The serum Tg level of the 105 patients who were negative for Tg antibody and had undergone previous ablation of thyroid tissue, was 2 ng/ml or higher after thyroid hormone withdrawal, and 91 (87%) of them had a serum Tg level of 2 ng/ml or higher after rhTSH stimulation. To evaluate the possibility of detect thyroid remnant or cancer based on the rhTSH-stimulated Tg levels, Tg was measured during thyroid hormone therapy after rhTSH stimulation in 46 patients with radioiodine uptake in the thyroid bed and 30 patients with metastatic disease diagnosed on the basis of a posttherapy scan with uptake outside the thyroid bed. Using a Tg cut-off level of 2 ng/ml, rhTSH stimulated Tg level greater than 2 ng/ml predicted disease in 52% of the patients with uptake limited to the thyroid bed and 100% of the patients with uptake outside the thyroid bed.

A large non-randomized, retrospective study was published following these prospective randomized trials [14]. That study examined 289 patients with differentiated thyroid cancer, and all patients had the choice of having the DxWBS performed after thyroid hormone withdrawal or after rhTSH administration while still on thyroid hormone therapy, and the result was two groups of patients: 161 in which DxWBS was obtained after TH withdrawal and 128 in which it was obtained after rhTSH. The two groups were comparable in terms of patient and tumor characteristics. The DxWBS scans were negative in 66 (52%) of the rhTSH patients and 40 (25%) of the TH withdrawal patients. The numbers of patients with evidence of uptake on the DxWBS following rhTSH (33%) and TH withdrawal (35%) were similar. Thyroid bed uptake was significantly more common in the TH withdrawal group (40%) than in rhTSH group (15%). Eleven patients (4 in the rhTSH group and 7 in the TH withdrawal group) with evidence of metastatic disease had only thyroid bed uptake on DxWBS. This study investigated the positive and negative predictive values as well as sensitivity and specificity of both DxWBS and Tg with elevated TSH. The sensitivity, specificity, and positive and negative predictive value of these tests was uninfluenced by either preparation. The combined results of the DxWBS and stimulated Tg yielded higher sensitivity for disease detection.

Many studies have been published in addition to these large trials [15–19], but they did not directly compare Tg and DxWBS following rhTSH administration and TH withdrawal, and only confirmed the safety or efficacy of rhTSH in monitoring thyroid cancer patients. The results of all of these studies supported the use of rhTSH instead of TH withdrawal for Tg and DxWBS assessment in patients with differentiated thyroid cancer.
2. Diagnostic use of rhTSH in the evaluation of disease status: thyroglobulin monitoring alone

Monitoring the stimulated Tg level and DxWBS have been routinely performed to detect differentiated thyroid cancer. Some thyroid specialists currently advocate monitoring the stimulated Tg level alone for the detection of recurrent or persistent disease in low-risk patients. Cailleux et al. found no correlation between the DxWBS and the Tg level after withdrawal of TH and confirmed that the DxWBS suggests only the completeness of thyroid ablation [20]. They concluded the serum Tg level after withdrawal of TH is more sensitive for disease detection than DxWBS. These findings were confirmed by Pacini et al. [21]. They studied 315 patients with differentiated thyroid cancer, who, at the first control DxWBS after thyroid ablation, had undetectable serum Tg level in the hypothyroid state. DxWBS was negative in 225 patients, and in 90 patients the scan was positive only in the thyroid bed. After a mean period follow-up of 12 years, 281 (89.2%) patients had a complete remission, 29 (9.2%) had persistent thyroid bed uptake with undetectable Tg level in a hypothyroid state, and only 2 (0.6%) had local recurrence. The investigators concluded that DxWBS could be avoided in patients with undetectable serum Tg levels in the hypothyroid state. They reported similar results [22] when they retrospectively studied 72 patients with differentiated thyroid cancer by comparing rhTSH-stimulated Tg levels with the hypothyroid Tg levels and DxWBSs. The serum Tg levels remained undetectable after stimulation with rhTSH, in 41 (56.9%) of 72 patients, and 36 (87.8%) of the 41 patients had an undetectable Tg level when hypothyroid. DxWBS was negative in 83% of these 36 patients, and the other patients had low uptake in the thyroid bed. No patients with an undetectable rhTSH-stimulated Tg level had evidence of metastatic disease. Mazzaferrri and Kloos [23] confirmed and supported these results. They investigated 107 patients with differentiated thyroid cancer and found that 11 (10%) of them had persistent tumor. All these 11 patients had positive rhTSH-stimulated Tg, and none of them had a positive DxWBS. The rhTSH-stimulated Tg level had a sensitivity of 100%, negative predictive value of 100%, and positive predictive value of 55%. Several studies have also demonstrated the usefulness and accuracy of rhTSH-stimulated Tg levels for detection of recurrence. Several other studies have similarly demonstrated the accuracy of rhTSH-stimulated Tg values for detection of cancer recurrence [24, 25]. Additionally, a consensus report has been published recommending that rhTSH-stimulated Tg levels alone are adequate for follow-up in low-risk patients with undetectable Tg levels on TSH suppression therapy [26]. Robbins et al. [27] found a stimulated Tg value greater than 2 µg/L to be excellent detecting persistent disease in a low-risk patients subgroup. However, in the total unselected group of patients undergoing surveillance, 13% of the patients with a stimulated Tg value less than 2 µg/L had evidence of recurrent disease identified by other imaging modalities. Pacini et al. showed that rhTSH-stimulated Tg combined with ultrasound examination of the neck provided a higher sensitivity and negative predictive value than the rhTSH-stimulated Tg test alone for detection of persistent/recurrent differentiated thyroid carcinoma [28]. These authors found rhTSH-stimulated Tg values alone to have excellent sensitivity (85%) for disease detection. When combined with neck ultrasound, sensitivity rose 96.3% with a negative predictive value of 99.5%.

3. Adverse reactions

The most commonly reported adverse events in the two Phase III clinical trials [12, 13] were nausea (11%), headache (7%), asthenia (3%), and vomiting (2%). There were several reports of hypersensitivity reactions including urticaria, rash, pruritis, flushing, and respiratory difficulties. No patients in controlled clinical trials developed antibodies to rhTSH. The surge in TSH level has the potential to promote rapid tumor edema and/or growth. According to the manufacture, among 55 patients with central nervous system metastases who were enrolled in the rhTSH compassionate use protocol, 4 developed complications, including hemiparesis, hemiplegia, or headache after rhTSH injection, attributed to local edema and/or focal hemorrhage within the tumor. In addition, one patient with metastasis to the optic nerve developed acute visual loss within 24 h after rhTSH administration. Severe dysphagia, secondary to laryngeal edema and requiring tracheotomy has been reported within 24 h after rhTSH administration to a patient with metastasis to the paratracheal area.
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Summary

In the past, routine monitoring of patients with differentiated thyroid carcinoma consisted of measurement of serum Tg level and whole body scanning with radioiodine, both of which require a hypothyroid state. RhTSH makes both tests possible for routine surveillance without making patients hypothyroid. Large trials have confirmed that DxWBS after rhTSH stimulation and serum Tg levels are as efficient for detection of recurrent differentiated thyroid carcinoma as these tests performed in the hypothyroid state. RhTSH-aided monitoring has recently become the standard method of surveillance for patients with differentiated thyroid carcinoma in many countries. However, rhTSH is used only after total thyroidectomy to monitor such patients. Numerous efforts have been made in many countries to improve the mortality rate and recurrence rate in patients with differentiated thyroid carcinoma. Total or near-total thyroidectomy with 131I ablation has been the global standard for treating patients with differentiated thyroid carcinoma. However, as described above, most endocrine surgeons in Japan prefer less than total thyroidectomy for differentiated thyroid cancer. It is necessary to compile guidelines for differentiated thyroid carcinoma in Japan on the initiative of Japan Thyroid Association and related associations.

References

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