Role of Recombinant Human Thyrotropin (rhTSH) in the Treatment of Well-Differentiated Thyroid Cancer

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Abstract Since the introduction of radioiodine (RAI) for treatment of well-differentiated thyroid cancer (DTC) more than 50 years ago, prolonged periods of hypothyroidism were routinely used as part of the treatment regimen. Recombinant human TSH (rhTSH) was introduced in the 1990s as a tool to elevate the serum TSH without the need for thyroid hormone withdrawal and symptomatic hypothyroidism. After being initially approved as a diagnostic tool for use in RAI scanning and stimulated thyroglobulin testing, rhTSH was approved as an adjunct to RAI remnant ablation in patients without distant metastases in Europe in 2005 and in the US in 2007. Following successful use of rhTSH for diagnostic purposes, it has been extensively studied for use with therapeutic doses of RAI in the setting of RAI remnant ablation and is now an integral part of DCT therapy. The use of rhTSH in clinical practice in the last decade was coupled with the growing interest in an individualized, risk-stratified approach to the management of patients with DCT. While traditional treatment for DTC included surgery and RAI therapy for all patients, many more recent studies demonstrated the value of selective use of RAI only in patients who will probably benefit from treatment. This manuscript reviews the evolving role of rhTSH in the current risk adapted climate of thyroid cancer management with particular emphasis on the use of rhTSH as an aid to RAI therapy.

Keywords Thyroid cancer · Recombinant human thyrotropin · Thyroid hormone withdrawal · Remnant ablation · Adjuvant therapy

Introduction

Since the introduction of radioiodine (RAI) for treatment of well-differentiated thyroid cancer (DTC) more than 50 years ago, prolonged periods of hypothyroidism were routinely used as part of the treatment regimen. The withdrawal of thyroid hormones causes elevation of thyrotropin (TSH), which stimulates RAI uptake in DTC cells and enhances RAI treatment efficacy. The withdrawal of thyroid hormone causes iatrogenic hypothyroidism with significant symptoms including lethargy, constipation, weakness, myalgia, and mood disturbances [1, 2]. Despite the significant side effects of THW, this practice is safe and severe adverse events are rare.

Recombinant human TSH (rhTSH) was introduced in the 1990s as a tool to elevate the serum TSH without the need for thyroid hormone withdrawal and symptomatic hypothyroidism. As compared with THW, rhTSH is well tolerated with only minor side effects that may include nausea and headaches. After being initially approved as a diagnostic tool for use in RAI scanning and stimulated thyroglobulin testing in the US In 1997, rhTSH was approved as an adjunct to RAI remnant ablation in patients without distant metastases in Europe in 2005 and in the US in 2007. Following successful use of rhTSH for diagnostic purposes, it has been extensively studied for use with therapeutic doses of RAI in the setting of RAI remnant ablation and is now an integral part of DCT treatment (Table 1).

The use of rhTSH in clinical practice in the last decade was coupled with the growing interest in an individualized, risk-stratified approach to the management of patients with DCT [3, 4]. While traditional treatment for DTC included surgery and RAI therapy for all patients (“one size fits all” approach), many more recent studies demonstrated the value of selective use of RAI only in patients who will probably benefit (in terms of recurrence and mortality) from

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Table 1 Clinical use of rhTSH

	Modality	Usual RAI activity (mci)	Approved ^a
^a By the regulatory agencies in the US, Europe, and other countries ^b Higher activities can be used following dosimetry	Diagnostic	Diagnostic RAI scanning	2–5
		Stimulated thyroglobulin measurement	None
	Therapy	Remnant ablation	30–100
		Adjuvant therapy	100–150
		Therapy of metastases/gross residual disease	100–200 ^b

treatment. In this manuscript, we will review the evolving role of rhTSH in the current risk adapted climate of thyroid cancer management with particular emphasis on the use of rhTSH as an aid to RAI therapy.

Radioiodine Uptake with THW versus rhTSH

Although rhTSH and endogenous TSH have similar effects on thyroid cells, the method of TSH stimulation affects the iodine kinetics in both thyroid tissue and the whole body. This is mainly due to the difference in thyroid hormone status between the two methods. Treatments using rhTSH are done in patients in either a euthyroid or iatrogenic thyrotoxic state (due to concurrent levothyroxine administration) while THW approaches require the patient to be clinically hypothyroid. Because radioiodine is principally excreted by the kidneys, and hypothyroidism is associated with significant decrease in glomerular filtration rate and cardiac output, THW is associated with marked increase in whole body RAI retention times. With the use of rhTSH, the higher renal clearance of radioiodine during euthyroidism reduces the mass of iodide available for transport into thyroid tissue. The reduced RAI uptake in euthyroid patients is partially compensated for by a significantly increased half-time within the thyroid cancer cells [5]. This may be explained by the favorable pattern of rhTSH stimulation producing a high and transient peak of TSH levels. The increased in-cell half time of I131 in the rhTSH group probably does not fully compensate for the lower uptake, and the mean remnant RAI exposure is lower in rhTSH treated patients [5]. The biologic significance of this small difference is unknown, and the practical comparison of the two methods relies mostly on clinical outcome data. It is important to note that due to the faster urinary excretion of RAI associated with rhTSH, there is a significantly reduced radiation dose to extra-thyroidal organs which may reduce radiation related side effects [6].

Post-operative RAI Therapy

Therapeutic use of radioiodine after thyroidectomy in patients with DCT has three general indications: 1- *Remnant*

ablation: destruction of residual normal thyroid tissue left in the neck following surgery, 2- *Adjuvant therapy*: destruction of subclinical microscopic areas of thyroid cancer remaining after surgery, and 3- *Treatment of gross disease*: treatment of clinically apparent residual or metastatic thyroid cancer [7]. These indications often overlap, as in cases in which RAI is given for remnant ablation, but on the post-therapy scan lateral neck uptake is detected, representing metastatic lymph nodes. In such cases RAI serves both as remnant ablation and as adjuvant therapy. A clearer understanding of the specific indications for treatment will improve our ability to select patients most likely to benefit from RAI after thyroidectomy, and will influence the choice of administered activity.

Thyroid Remnant Ablation

Indication and Rationale

Thyroid remnant ablation is used following surgery to destroy normal thyroid tissue left in the neck after total thyroidectomy. Ablation of thyroid residual tissue may facilitate the follow-up by eliminating thyroglobulin (TG) production and RAI uptake by normal thyroid tissue, permitting the early detection of recurrence based on serum TG measurement and/or RAI WBS. Additionally, the post-therapy scan obtained at the time of remnant ablation may facilitate initial staging by identifying previously undiagnosed disease.

In recent years the rationale of performing routine remnant ablation in low risk patients to facilitate follow-up has been questioned. First, in patients treated without remnant ablation with low level detectable TG on levothyroxine suppression, the use of serial measurements can reveal changes over time and may indicate disease progression during long term follow-up. Second, the use of ultrasound, which is relatively inexpensive, widely available, and associated with no risk in terms of radiation exposure, has become the primary follow-up testing modality in most patients with DTC [8]. In low risk patients, sonography has been shown to identify persistent or recurrent disease earlier and with higher sensitivity than serum TG measurements or RAI scanning [9]. Its negative predictive value is also very high, and when combined with US-guided fine-

needle aspiration (FNA) biopsy, it is the best diagnostic tool available today for disease recurrent/persistence. Therefore, neck US can be used effectively to detect recurrent disease without having to subject all low risk patients to RAI remnant ablation.

In contrast to high risk patients in which RAI therapy (adjuvant or treatment of gross disease) has been shown to decrease recurrence and mortality, in low risk patients such benefit has not been shown [10, 11]. The National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) evaluated outcome of 2936 patients after a total thyroidectomy with or without RAI therapy after median follow-up of 3 years [12]. While they demonstrated improved overall survival with RAI therapy in patients with stage III and IV disease (NTCTCSG staging criteria are similar but not identical to the AJCC criteria), and also some benefit in patients with stage II disease, there was no impact of RAI therapy in patients with stage I disease. Vaisman et al. [13] reported of 289 patients treated with lobectomy or total thyroidectomy without RAI remnant ablation. After a 5-year median follow-up, structural disease recurrence was detected in 2.3% (5/217) of patients treated with total thyroidectomy alone, and in 4.2% (3/72) of patients treated with thyroid lobectomy. These numbers are low and quite similar to those reported in cohorts of patients who received RAI remnant ablation after surgery [14].

Thus, the ATA guidelines do not recommended RAI ablation for the lowest risk patients who have unifocal or multifocal cancer <1 cm without other higher risk features. In patients with intermediate risk features (1–4 cm thyroid cancers confined to the thyroid, who have documented lymph node metastases, or other risk features) the recommendation is for selective use of RAI, according to individual risk assessment. These recommendations point to the fact that ablation is not necessary for follow-up facilitation, but rather targets patients who may benefit from the adjuvant effect of treatment. Table 2 presents the ATA framework for deciding whether RAI is worthwhile based on the AJCC classification, and provides the rationale for therapy and the strength of existing evidence for or against treatment.

Administered Activity for Remnant Ablation

Typical administered activities for RRA range from 30 to 100 mCi [7]. The goal is to administer the lowest activity possible that will effectively eliminate the residual normal thyroid tissue. Recently, a prospective randomized trial showed no difference in the successful ablation rate of patients prepared with rhTSH between those who received 50 mCi and those who received 100 mCi of RAI [15]. Results from two RCTs were recently presented in the International Thyroid Congress in Paris and in the 81st ATA annual meeting. The ESTIMABL trial from France

[16] and the British HiLo trial [17] encompassed almost 1,200 patients, and both compared 30mCi and 100mCi RAI activities for remnant ablation with either rhTSH or THW preparation. The results of both studies showed equal ablation success rates with either RAI dose and with either preparation method. Therefore, we recommend using administered activities between 30 and 50 mCi for routine ablation purposes.

THW versus rhTSH for RAI Remnant Ablation

Four randomized controlled trials (RCTs) [2, 18–20], one meta-analysis [21] several observational studies [22–26], and two unpublished RCTs (the ESTIMABL and HiLo studies) compared the efficacy of rhTSH-assisted and THW-assisted RAI remnant ablation. These studies have several methodological differences regarding T4 withdrawal duration, rhTSH regimen (with or without a short term T4 withdrawal), and RAI administered activities (30 to 100 mCi). The characteristics of the randomized trials are detailed in Table 3. Overall, there was no significant difference in successful ablation rates between rhTSH and THW, when “successful ablation” was evaluated in these studies using diagnostic WBS and/or stimulated TG at 6–12 months (Fig. 1). These outcomes represent successful destruction of normal thyroid tissue, and do not necessarily predict long term outcome in terms of recurrence. A recent study from our group addressed this issue, evaluating disease recurrence rates in 394 DCT patients over a median of 2.5 y after RAI remnant ablation [22]. Similar rates of recurrence (4% rhTSH vs. 7% THW) were seen in the 320 patients undergoing rhTSH-assisted RRA and the 74 patients prepared by THW.

The current guidelines by the ATA, ETA and NCCN support the use of rhTSH as an alternative to traditional THW for remnant ablation (recommendation grade A). The actual use of rhTSH for remnant ablation varies between countries on the basis of cost, health care delivery systems, and other details that are specific to each country.

RAI Therapy for Adjuvant Therapy

Indication and Rationale

While the goal of thyroid surgery for DCT is to remove all cancer tissue, in many cases microscopic thyroid bed or lymph node microscopic cancer foci may persist. In various series the incidence of microscopic LN involvement is as high as 50–70% if prophylactic neck dissections are done, which have uncertain clinical significant [3]. The role of adjuvant RAI therapy is to destroy occult areas of thyroid cancer after appropriate surgery in patients with higher risk

Table 2 The ATA recommendations for decision making in RAI administration

Factors	Description	Expected benefit			RAI ablation usually recommended	Strength of evidence
		Decreased risk of death	Decreased risk of recurrence	May facilitate staging and follow-up		
T1	1 cm or less, intrathyroidal or microscopic multifocal	No	No	Yes	No	E
	1–2 cm, intrathyroidal	No	Conflicting data ^a	Yes	Selective use ^a	I
T2	>2–4 cm, intrathyroidal	No	Conflicting data ^a	Yes	Selective use ^a	C
T3	>4 cm					
	<45 years old	No	Conflicting data ^a	Yes	Yes	B
	≥45 years old	Yes	Yes	Yes	Yes	B
	Any size, any age, minimal extrathyroidal extension	No	Inadequate data ^a	Yes	Selective use ^a	I
T4	Any size with gross extrathyroidal extension	Yes	Yes	Yes	Yes	B
Nx, N0	No metastatic nodes documented	No	No	Yes	No	I
N1	<45 years old	No	Conflicting data ^a	Yes	Selective use ^a	C
	>45 years old	Conflicting data	Conflicting data ^a	Yes	Selective use ^a	C
M1	Distant metastasis present	Yes	Yes	Yes	Yes	A

^a Because of either conflicting or inadequate data, no recommendation either for or against RAI ablation was given for these subgroups. However, selected patients within these subgroup with higher risk features may benefit from RAI ablation

of recurrence or death. When the first dose of RAI is being given as adjuvant therapy, recommended doses are between 100 and 150 mCi according to the ATA guidelines [7].

The use of RAI can be referred as adjuvant therapy when the combination of age, tumor size, lymph node status (number, size, presence of extranodal extension), and

individual histology (aggressive histologies, extensive vascular invasion) predicts an intermediate to high-risk of recurrence or death. In this group the likelihood of remaining thyroid cancer tissue left in the neck after surgery is high, and this first dose of RAI has a dual role of both remnant ablation and adjuvant therapy [27].

Table 3 RCTs comparing rhTSH versus THW for remnant ablation

Study	Year	Study Design				Outcome	
		Thyroid hormone withdrawal	rhTSH	I131 dosage	No. patients evaluated	Ablation according to diagnostic WBS ^a	Ablation according to stimulated TG ^b
Pacini et al. [20]	2006	4–6 w, TSH goal >25	0.9mcgX2	100 mci	60	rhTSH: 100% THW: 100%	rhTSH: 96% THW: 86%
Chianelli et al. [18]	2009	39 d T4 withdrawal, first 19 d with T3 therapy	0.9mcgX2	54 mci	42	rhTSH: 90.5% THW: 95.2%	rhTSH: 85% THW: 90%
Taieb et al. [19]	2009	5 w	0.9mcgX2	100 mci	71	rhTSH: 72.2% THW: 91.4%	rhTSH: 91.7% THW: 97.1%
Lee et al. [2]	2010	Two groups: 1. T4 withdrawal –4 w 2. T4 withdrawal –4 w, first 2 w with T3 therapy	0.9mcgX2+four days T4 withdrawal	30 mci	291	rhTSH: 94% THW: 94.2%	rhTSH: 92.8% THW: 91.4%

W weeks, d days, WBS whole body scan

^a 6–12 months after RAI ablation

^b Definition of successful ablation according to stimulated TG: Pacini et al.: < 2 µg/l, Chianelli et al.: < 1 µg/l, Taieb et al.: < 0.8 µg/l, Lee et al.: < 1 µg/l

Fig. 1 Remnant ablation success rate (%) with rhTSH vs. THW at 6–12 months. **a** Success rate according to whole body scan (WBS). **b** Success rate according stimulated TG

THW versus rhTSH for RAI Adjuvant Therapy

Most data regarding the efficacy of adjuvant therapy is included in studies evaluating remnant ablation. Only few studies performed subgroup analysis for patients with moderate risk of recurrence or for patients with uptake outside the thyroid bed on WBS. In a study by Pilli et al. [15] which evaluated the efficacy of RAI remnant ablation with 50mCi versus 100mCi using rhTSH preparation, a subset patients was identified in whom cervical lymph node metastases were detected on the post therapy scan. In this group RAI therapy was administered for remnant ablation, but served also as adjuvant therapy. Treatment success was defined as disappearance of both the thyroid bed uptake and lymph node uptake 6–8 month after treatment. Success rates were high whether treated with 50mCi or 100mCi RAI (86% and 80.5% respectively, $p=0.75$), demonstrating the efficacy of rhTSH-assisted RAI therapy in the setting of adjuvant therapy.

Our group recently reported the clinical outcome of 84 DTC patients in whom RAI-avid lesions outside the thyroid bed were first identified at the time of RAI remnant ablation [27]. In this series, rhTSH-stimulated RAI therapy resulted

in successful adjuvant therapy in 70% of patients prepared with rhTSH, compared with 55% of patients prepared with THW. Further, RAI-avid metastatic disease discovered at the time of rhTSH-stimulated remnant ablation was successfully treated in both locoregional lymph nodes (70% NED) and pulmonary parenchyma (75% NED).

According to these published studies, preparation with either rhTSH or THW appears to have similar adjuvant effects on small-volume RAI-avid disease identified at the time of initial therapy. It is on the basis of this cumulative body of data from multiple centers that rhTSH was approved in the US and Europe for both remnant ablation and adjuvant therapy, provided the patient doesn't have macroscopic distant metastases.

RAI therapy for Distant Metastases

Indication and Rationale

The use of RAI for the treatment of metastatic DCT is well established as an effective therapy, especially in patients with RAI avid pulmonary micronodular metastases [28, 29]. In a study by Maxon et al. [28] patients treated for RAI-concentrating pulmonary metastases had a five-year survival rate of 60%, compared with 30% in those whose tumors do not concentrate RAI. Long-term survival is highest in patients with pulmonary micro-metastases seen on ^{131}I scan, but not on cross sectional imaging. Skeletal metastases often do not concentrate ^{131}I very well, and complete resolution of disease occurs in fewer than 10% of treated patients, and partial remission in only 35% [30]. It is important to note that in recent years there is a trend toward a more selective use of empiric repeated ^{131}I administrations in the treatment of distant metastatic lesions [4], and once again clinicians are being encouraged to base their decision on a careful risk/benefit analysis. For example, metastatic lesions that are positive on FDG PET scanning are usually quite refractory to RAI therapy [31], since these tumors often are either FDG avid or ^{131}I avid, but not both.

The RAI activity administered can be given empirically or determined by either lesional or whole body dosimetry. Each approach appears effective with no single method being clearly superior to the others. Since dosimetry studies are usually restricted to specialized nuclear medicine centers, most patients with distant metastases have administered activities determined empirically. Typical empiric administered activities for known distant metastases range between 100 and 200 mCi depending on the age of the patient, the adequacy of bone marrow function as reflected by the complete blood count, RAI avidity of the disease, and renal/cardiac function of the individual patient.

THW versus rhTSH in Metastatic Disease

The early experience using rhTSH for patients with metastatic DTC was as part of a compassionate use program for selected patients that were unable to raise their TSH levels endogenously (hypothalamic or pituitary disorders) or in whom thyroid hormone withdrawal was contraindicated because of co-morbid conditions. In 1997, Rudavsky and Freedman [32] published the first report of off-label use of rhTSH-assist with RAI therapy in a patient with metastatic DTC. A summary of published data up to 2005 by Luster et al. [33] showed that in 115 patients with persistent or metastatic disease, 2% achieved complete remission, 36% partial response, and 27% disease stabilization. Robbins et al. [34] reported the effect of RAI treatment after rhTSH preparation as part of the Thyrogen Compassionate Use Program in 115 patients from the United States and Canada with metastatic disease. Response to therapy was seen in 75% of patients at 12 months, as assessed by the serum TG levels. In contrast to these reports, a few patients with metastatic disease have been reported in whom rhTSH did not result in satisfactory uptake of RAI into target lesions [35, 36]. Moreover, in a minority of patients with brain or bone metastases, administration of rhTSH was found to stimulate expansion of the tumor, with ensuing compression of key anatomical structures and neurological, skeletal or other clinical complications [33]. In these cases imaging studies usually show peritumoral edema, which often responds to glucocorticoid therapy.

We have recently published the first report evaluating five year overall survival rates in 175 thyroid cancer patients with RAI avid distant metastases, prepared with either traditional THW or a four-injection, rhTSH-stimulated, dosimetry-guided treatment protocol. The protocol included two rhTSH injections followed by whole blood dosimetry, and a week later two additional rhTSH injections followed by administration of high doses RAI (determined by the dosimetry results). After a median follow-up of 5.5 year, there were no significant differences in overall survival between patients prepared for RAI therapy with rhTSH alone, THW alone, or THW followed by rhTSH. In a multivariate analysis that included clinicopathological features and method of preparation (rhTSH or TWH), only age at diagnosis was an independent predictor of overall survival. It is important to note that the treatment protocol used in this study using four rhTSH injections and dosimetry based therapy is not widely available and is very expensive.

The small volume of available data, coupled with the observations that rhTSH preparation is associated with more rapid clearance of RAI from the body [5] and possibly lower radiation doses to metastatic lesions [37, 38], indicate that additional studies are needed before rhTSH can be routinely recommended as an alternative for THW in known metastatic

disease. Its use should be currently limited to special circumstances, such as in patients who are unable to elevate TSH sufficiently or with severe comorbidities.

Summary

The use of rhTSH as replacement to iatrogenic hypothyroidism has made a huge difference in the lives of patients with thyroid cancer. It is a potent stimulator of thyroid derived cells, and is currently in routine use for thyroid patients without distant metastases. Studies are ongoing to further define its role in the treatment of metastatic disease and its use with advanced imaging techniques.

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