INVITED REVIEW

Clinical use of recombinant human TSH in thyroid cancer patients

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Abstract

Recombinant human TSH (rhTSH) is an effective and safe alternative to thyroid hormone withdrawal during the post-surgical follow-up of papillary and follicular thyroid cancer. Its clinical efficiency for the detection of persistent and recurrent disease is similar to that of thyroid hormone withdrawal. The main purpose for its use is to avoid hypothyroidism.

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Introduction

The reason behind the follow-up of patients with papillary and follicular thyroid carcinoma is the early detection of persistent or recurrent disease. This is made possible through the use of serum thyroglobulin (Tg) determination or total body scanning with ¹³¹I (¹³¹I-TBS), or a combination of both tests (1–3).

Extensive clinical experience has led to increasingly wide acceptance of serum Tg measurement as the most sensitive and least invasive modality for the follow-up of papillary and follicular carcinoma after total thyroidectomy and ¹³¹I ablation. In the absence of circulating thyroid antibodies, serum Tg measurement is usually very well correlated with clinical status. Following thyroid hormone withdrawal, Tg is detectable in the serum of almost all patients with persistent or recurrent disease, only very few patients with small lymph node metastases in the neck have undetectable Tg levels. When compared with ¹³¹I-TBS, serum Tg measurement has the advantage of detecting non-functioning metastases not visible on ¹³¹I-TBS. However, both ¹³¹I uptake and Tg release by normal and tumoral thyroid tissues is a TSH-dependent process. During thyroid hormone suppressive therapy, even with the use of a sensitive assay, serum Tg concentration is suppressed to undetectable levels in about 20% of patients with lymph node metastases in the neck, and in 5% of patients with small distant metastases, not visible on standard X-rays.

Similarly, the results of ¹³¹I-TBS depend on the intrinsic ability of thyroid cancer tissue to take-up ¹³¹I in the presence of high serum TSH concentrations. In

large clinical series, ¹³¹I uptake was found in only two-thirds of metastatic patients (1–3).

Thus, both procedures, to be effective, require elevated serum TSH levels above some arbitrary figure such as 25 or 30 mU/l (1).

Standard protocols for TSH stimulation

In clinical practice, this condition is obtained by withdrawing L-thyroxine (L-T4) suppressive therapy for 4–6 weeks. However, the resultant hypothyroidism is poorly tolerated by some patients. This problem can be attenuated by substituting the more rapidly metabolized triiodothyronine (L-T3) for thyroxine for 3 weeks, and then withdrawing it for 2 weeks. Even if L-T3 substitution is used, patients may experience a wide range of hypothyroid signs and symptoms which may be severe and may result in a substantial impairment of the patients' lives and ability to work (4), and occasional tumor growth. Another alternative is simply to reduce the daily dosage of L-T4 by 50% for 3–4 weeks (5); however, no study has yet confirmed the efficiency of this method.

Past experience with exogenous TSH

In the past, intramuscular administration of bovine TSH (bTSH) (10 IU/day for 3 consecutive days) has been successfully employed to stimulate radioiodine uptake in metastatic patients, without the need of withdrawing thyroid hormone therapy (6). However, bTSH was less effective than endogenous TSH (7), and was associated

with adverse reactions, including nausea, vomiting, local induration, urticaria, and anaphylactic shock (8). In addition, its repeated use could result in a loss of potency that was related to the development of neutralizing antibodies (9). For all these reasons, and also because it was extracted from bovine pituitary glands, the use of bTSH has been abandoned. Similarly unsuitable is the potential use of human TSH (hTSH), recovered and purified from pooled pituitary glands obtained at autopsy, due to the possible transmission of Creutzfeldt–Jakob disease, as observed in patients treated with hGH (10).

Production of recombinant human TSH

Recombinant human TSH (rhTSH) has been developed to meet the need for safe, adequate exogenous TSH stimulation in patients with papillary and follicular thyroid carcinoma (Table 1). TSH is a pituitary heterodimeric glycoprotein composed of an α -subunit common to gonadotropins and a hormone-specific β -subunit. Once the β -subunit of the human TSH gene had been cloned (11), the encoded protein could be overexpressed in a cell system (Chinese hamster ovary cells), by transfection with the human α - and β -subunits of complementary or genomic DNA. With this technique, large quantities of highly purified rhTSH can be obtained (12). Its bioactivity and metabolic clearance seem to be affected by the pattern of post-translational glycosylation.

The pharmacokinetics of rhTSH have been studied in patients with differentiated thyroid carcinoma who received a single intramuscular injection of 0.9 mg rhTSH: the mean peak rhTSH concentration of 116 ± 38 mU/l is reached in 3–24 h (mean: 13 ± 8 h). The mean elimination half-life is 22 ± 8 h and the mean clearance rate is 36 ± 12 ml/min.

In vitro studies have shown that rhTSH can effectively stimulate cAMP production in a rat thyroid cell line (FRTL5 cells), and can promote the growth of human

fetal thyroid cells (13). The *in vivo* biological efficacy of rhTSH was then demonstrated in monkeys, in which it was able to increase serum T3 and T4 concentrations and stimulate thyroidal radioiodine uptake (14). A single 0.1 mg dose of rhTSH is a potent stimulator of thyroid function in normal human volunteers: serum T3 concentrations rose slightly earlier than serum T4 concentrations, at 4 h and 8 h, respectively, and the rise in serum Tg was delayed until approximately 24 h. The decline in endogenous TSH, 7 days after rhTSH injection, is due to a feedback suppression secondary to the rhTSH-induced increases in circulating T4 and T3. The incremental increase in Tg was greater than that in either T3 or T4, and the increase in serum T3 was slightly greater than that in T4 (15).

Diagnostic use of rhTSH: results of clinical trials in thyroid cancer patients

The availability of large quantities of rhTSH prompted clinical trials in patients with papillary and follicular thyroid cancer to investigate its safety and efficacy in promoting radioiodine uptake and Tg secretion.

A first study (phase I/II) was completed in 1994 in 19 patients after a recent thyroidectomy for differentiated thyroid cancer (16). The study protocol compared the stimulation of ^{131}I uptake and of Tg release in the serum after rhTSH administration (0.9–3.6 mg (10–40 U) for 1–3 days) and after withdrawal of T3. rhTSH injections were well tolerated: minor side effects, nausea and vomiting, were observed in a few patients who received the highest doses of rhTSH. The quality of life was maintained during rhTSH and decreased after T3 withdrawal. The quality of total body scans and the number of sites of abnormal uptake coincided in rhTSH and in hypothyroid scans in 12 (63%) patients. Additional sites of uptake that were not visible on the hypothyroid scan were identified in three (16%) patients after rhTSH. In three (16%) other patients, some lesions were seen exclusively on the hypothyroid scan. Serum Tg levels increased more than 2-fold in response to rhTSH in 73% of the patients. However, the increase was quantitatively lower after rhTSH than after T3 withdrawal in 93% of the patients.

The encouraging results of this limited study were confirmed in a larger multicentric phase III study conducted between 1992 and 1995 in the USA in 127 patients (17). In this trial, patients underwent two total body scans: the first after two injections of rhTSH (0.9 mg per day for 2 consecutive days) while continuing L-T4 therapy, and the second after thyroid hormone withdrawal. The quality of life of patients was maintained and was significantly better after rhTSH than during hypothyroidism; however, the overall effectiveness of rhTSH was below that of hypothyroidism. Among scan-positive patients ($n=62$), rhTSH-stimulated scans were equal to those obtained after withdrawal of L-T4 in 66%, superior in 5% and inferior

Table 1 Rationale for the use of rhTSH in the follow-up of thyroid cancer patients.

Potential benefits

Effectiveness for stimulating ^{131}I uptake and Tg production.
Avoidance of hypothyroidism and improvement of quality of life.
Safety: side effects are minimal and no anti-rhTSH antibodies have been found.

Potential problems

Sensitivity of ^{131}I scanning and of serum Tg measurement may be lower than following thyroid hormone withdrawal.

The absence of decline in renal clearance may lower total body exposure, but a higher activity of ^{131}I may be required for the delivery of efficient radiation doses (this may necessitate dosimetry).

The risk of stimulating progression of cancer, potentially decreased by rhTSH due to shorter exposure of tumor to TSH, still persists.

in 29% of cases. Serum Tg concentrations increased in 14 patients after L-T4 withdrawal and in 13 patients after rhTSH stimulation, out of 35 patients for whom Tg analysis was available. A possible limitation of this study was that half of the patients had uninformative negative scans, and 72% of those with positive scans had uptake limited to the thyroid bed. Only 17 patients had evidence of local or distant metastases. Other limitations were that the diagnostic dose of ^{131}I had not been fixed for scanning and ranged from 74 to 148 MBq (2–4 mCi), and serum Tg measurement was not an end-point of the study. It also appeared that the bioavailability of ^{131}I was lower in euthyroid patients after rhTSH stimulation than in hypothyroid patients after withdrawal of thyroid hormone therapy, due to the reduction of renal clearance of ^{131}I during hypothyroidism. This increases body retention of ^{131}I in the hypothyroid phase by a factor of approximately 2, compared with the euthyroid phase, and results in an increase in whole body radiation but also in the bioavailability of ^{131}I (Table 3 and Fig. 1). This clinical experience highlights the importance of administering adequate activities of ^{131}I , i.e. 4 mCi (148 MBq) or more, when scanning euthyroid patients. Available studies suggest that stunning, a phenomenon in which administration of a diagnostic activity of ^{131}I may impair the uptake of a subsequent therapeutic activity of radioiodine by thyroid tissue (18), is unlikely to occur with an activity of 4 mCi.

A second phase III multicentric trial, which included US and European centers, was then completed. It was designed to compare two different dosing regimens of rhTSH and to overcome the limitations of the previous studies (19). The results of this trial can be summarized as follows: 229 patients were randomly assigned to receive two injections of 0.9 mg rhTSH for 2

Table 2 Recommended ^{131}I scanning parameters after rhTSH (0.9 mg per day $\times$ 2, i.m.).

Sufficient diagnostic activity: 148 MBq (4 mCi) ^{131}I administered 24 h after the second rhTSH injection.

Appropriate equipment: For ^{131}I -TBS, a large field of view gamma camera and a high energy collimator should be used. For quantitative imaging, the best solution consists in the simultaneous anterior and posterior image acquisition with a dual-headed gamma camera.

Scanning performed 48 or 72 or even 96 h after the administration of the diagnostic activity of ^{131}I , and 4–7 days after the administration of therapeutic activities of ^{131}I .

Sufficient scanning time for total body scanning: 30 min or minimum counts: 140 000. For spot images, minimum scanning time: 10 min or minimum counts: 60 000, when using a large field of view gamma camera.

Reduction of the risk of artifacts: have the patient drink large amounts of liquid and lemon juice, chew gum, change clothes, and take a shower before scanning.

Absence of iodine contamination. Pregnancy excluded.

Measure serum thyroglobulin 48 to 72 h (and even later) after the last rhTSH injection.

Table 3 Biological and isotopic data in a metastatic patient from the multicentric study (19). ^{131}I uptake in vertebral metastasis (see Fig. 1), and total body retention were measured 48 h after the administration of 148 MBq (4 mCi), following stimulation with either rhTSH or withdrawal of thyroid hormone therapy. ^{131}I uptake in metastasis was also measured 96 h after the administration of 3.7 GBq (100 mCi).

		TSH ($\mu\text{U/ml}$)	Tg (ng/ml)	^{131}I -TBS	
				Uptake (%)	Retention (%)
Pre-study		<0.01	50		
rhTSH	48 h	56	81	0.2	3.2
	72 h	17	100		
Withdrawal		33	261	1.6	10.3
Therapy		–	–	0.6	–

consecutive days or three injections of 0.9 mg rhTSH, 3 days apart; ^{131}I was administered on the day following the last injection of rhTSH. Then, patients were studied again after withdrawal of thyroid hormone. The ^{131}I tracer dose was fixed at 148 MBq (4 mCi), scanning procedures were standardized (Table 2) and serum Tg evaluation was an integral part of the study. Serum Tg level was measured in a central laboratory with a radioimmunoassay method, and the clinical threshold of significance was assessed at 2 ng/ml.

Scans were similar after rhTSH and thyroid hormone withdrawal in 92% of the patients, with no apparent difference between the two dose regimens investigated. The diagnostic value of Tg measurement and of ^{131}I -TBS or of a combination of both tests were analysed according to disease stage.

In 46 patients with persistent ^{131}I uptake in the thyroid bed, the serum Tg level was >2 ng/ml in 22% during L-T4 therapy, in 52% after rhTSH and in 56% after withdrawal. Following rhTSH stimulation, when the results of ^{131}I -TBS and post-rhTSH Tg levels were combined, the detection rate increased to 94%.

Among the 30 patients with persistent or recurrent disease (defined as post-therapy scans with uptake outside the thyroid bed), 80% had concordant scans, 4% had superior rhTSH scans and 16% had superior withdrawal scans. Interestingly, serum Tg levels were >2 ng/ml in 80% during L-T4 therapy, and in 100% following either rhTSH stimulation or withdrawal of thyroid hormone treatment. The peak Tg levels were observed 2–3 days after the last injection of rhTSH. Quantitatively, the Tg level reached after rhTSH stimulation was in general lower than that obtained after thyroid hormone withdrawal (Table 3).

Quality of life was again maintained and was significantly better during rhTSH than during hypothyroidism induced by thyroid hormone withdrawal, and side effects were minimal, mainly consisting of mild and transient nausea or headache in less than 10% of patients. No patient developed detectable anti-rhTSH

Figure 1 ^{131}I -TBS obtained in a patient with a single bone metastasis, in a dorsal vertebrae. Quantitative data are given in Table 3. ^{131}I -TBS was obtained 48 h after the administration of 148 MBq (4 mCi) and stimulation with either rhTSH (A) or withdrawal of thyroid hormone therapy (B). ^{131}I -TBS was also obtained 96 h after the administration of 3.7 GBq (100 mCi), and withdrawal of thyroid hormone therapy (C).

antibodies, even after receiving repeated courses of rhTSH.

Altogether these clinical trials have clearly shown that rhTSH is an effective and safe alternative to thyroid hormone withdrawal during the post-surgical follow-up of papillary and follicular thyroid cancer.

Diagnostic use of rhTSH: follow-up after initial treatment

Traditional strategy

Three months after initial treatment, patients would undergo serum Tg determination on L-T4 treatment. Serum Tg testing should employ an immunoradiometric assay (IRMA) with a sensitivity of $<1\text{ ng/ml}$; interferences due to anti-Tg antibodies may lead to falsely low or undetectable values, and serum samples should be screened for anti-Tg antibodies with a sensitive assay, or should be subjected to a recovery test. False negative Tg measurements have been observed in this situation in about 20% of patients with isolated lymph node metastases in the neck and in 5% of patients with small distant metastases, mainly in lungs, not visible on X-rays (1–3).

Therefore, a diagnostic ^{131}I -TBS (1–5 mCi) and a serum Tg determination are usually performed after thyroid hormone withdrawal, 6–12 months after initial treatment. In patients with undetectable Tg levels during thyroxine suppressive therapy and with no evidence of disease, this is aimed to ensure that ablation is total and to search for persistent or recurrent disease. However, the yield of routine control diagnostic ^{131}I -TBS is very low; in a recent study on 256 consecutive patients who had a control ^{131}I -TBS and a serum Tg measurement following thyroid hormone withdrawal, 6–12 months after total thyroidectomy and ^{131}I ablation, a low uptake was found in the thyroid bed in 8%, and no focus of uptake was found outside the thyroid bed; the serum Tg level was undetectable in 82% of patients, among whom 0.9% experienced a clinical recurrence during the subsequent years. The Tg level was detectable in the other patients, and was above 10 ng/ml in 15 patients, among whom 33% experienced a clinical recurrence (20). It should be emphasized that after ^{131}I ablation the clinical relevance of persistent low uptake in the thyroid bed is under no circumstances demonstrated. Furthermore, in this study recurrences were identified by ^{131}I -TBS performed with a high activity of ^{131}I (i.e. 3.7 GBq) or

Figure 2 Protocol of follow-up based on the use of rhTSH and, as the first line test, serum thyroglobulin measurement. *This interval depends on Tg level and on the clinical context. An alternative is to give a diagnostic amount of ^{131}I immediately after the Tg result, taking advantage of the rhTSH injections. **The Tg threshold should be determined after rhTSH stimulation for each assay method.

other imaging modalities, but in no case by routine diagnostic ^{131}I -TBS.

New strategy using rhTSH

rhTSH stimulation permits the measurement of serum Tg in a condition of increased sensitivity with respect to L-T4 treatment during which serum TSH level is either low or undetectable (Fig. 2). In the confirmatory phase III trial, all patients with persistent or recurrent disease had detectable Tg levels after rhTSH stimulation. Although the number of metastatic patients reported is still limited, the data suggest that rhTSH-stimulated serum Tg should firstly be determined, with subsequent ^{131}I -TBS performed only in those patients whose serum Tg level becomes detectable after rhTSH stimulation. Patients with undetectable Tg levels following rhTSH may be considered cured; they should be followed up annually on L-T4 treatment and no other test is necessary, so long as serum Tg remains undetectable. However, where serum Tg levels change from undetectable during L-T4 treatment to detectable after rhTSH the presence of disease is indicated; this warrants a complete check-up, starting with a ^{131}I -TBS. Since the

optimal time for administering the ^{131}I activity is 24 h after the second injection of rhTSH (on day 3), and as serum Tg level can be measured in less than 24 h, the rhTSH stimulation given for Tg measurement can be used for ^{131}I scanning, and the diagnostic activity can be administered readily on day 4. Unfortunately, preliminary data indicate that in some patients serum Tg starts to increase only at day 4 or 5, or even later. This is too late for administering the diagnostic activity of ^{131}I , and a second course of rhTSH, or a withdrawal of thyroid hormone therapy will be necessary before administering ^{131}I .

A possible dilemma is where rhTSH-stimulated Tg is detectable but at a low level, i.e. 1–5 ng/ml. The clinical significance of these low Tg values (persistent disease vs normal thyroid remnant), as well as the prognostic relevance, remain to be determined. A ^{131}I -TBS is advisable in such patients, even though a large proportion will be negative.

Where measured serum Tg levels are above an institution's recommended threshold, in the range that is highly likely to indicate metastatic disease, a sensitive ^{131}I -TBS performed with a large activity of ^{131}I (3.7 GBq or more), is probably warranted (1–3). The institutional threshold of Tg, above which a sensitive ^{131}I -TBS should be performed must be determined for each available method of Tg measurement. At the present time, the administration of a large activity of ^{131}I should be performed after withdrawal of thyroid hormone treatment rather than after rhTSH stimulation.

Therapeutic use of rhTSH: the 'compassionate use program'

Withdrawal of L-T4 suppressive therapy in preparation for ^{131}I therapy may expose patients with metastases in critical body structures such as vertebrae or the brain to severe neurological complications (21). In addition, a small minority of patients may not be able to elicit a sufficient rise of endogenous TSH after thyroid hormone withdrawal, due to older age, long-term suppressive therapy, concomitant illness, other treatments with drugs such as corticosteroids, or to pituitary insufficiency, which prevents adequate uptake of ^{131}I in metastatic foci. Finally, withdrawal of thyroid hormone therapy may be contraindicated for medical reasons, such as ischemic heart disease or myxoedema madness. In such conditions, it has been possible to deliver radioiodine therapy following exogenous stimulation by rhTSH within the framework of a clinical protocol called the 'compassionate use program'. Several hundreds of patients suffering from one of these conditions have been treated in the framework of this program in the USA and Europe since April 1995. Although a detailed, comprehensive review of the results of this program is not currently available, our own experience and the few reports published (22–26) indicate that it is possible to deliver high radiation

doses with ^{131}I to metastatic thyroid cancer by using rhTSH. From a dosimetric point of view, it is likely that the ^{131}I activity administered will have to be higher, due to the more rapid clearance of ^{131}I in euthyroidism compared with hypothyroidism, although quantitative dosimetric studies are not yet available.

Neurological complications due to tumor growth, edema or hemorrhage occurred in some patients with cerebral or spinal metastases (26). In some patients, swelling and pain due to bone metastases were observed. However, the duration of symptoms was shorter than expected with therapy administered during hypothyroidism. This may be related to a shorter duration or to a less intensive stimulation of thyroid neoplastic tissues, but in any case this warrants caution, and corticosteroid therapy is recommended in patients with metastases in critical body structures. At this stage, it is not possible to report on the long-term benefits of this treatment, especially given that most patients treated in this way had large tumor masses or end-stage disease, and the expected benefits in these patients were indeed limited. No study has been carried out in patients with small metastases, and the relevance of rhTSH stimulation for the treatment of metastatic disease has yet to be proven (23–25).

In the rare thyroid cancer patients with pituitary insufficiency, the use of rhTSH proved to be useful for ^{131}I scanning, but again it is not possible to report on the long-term benefits of this treatment.

In some patients, serum TSH does not reach an adequate level following thyroid hormone withdrawal. This is observed mainly in elderly patients or after long-term suppressive L-T4 treatment. The use of rhTSH has been advocated in these patients to provide adequate TSH stimulation. However, ^{131}I uptake in metastases will remain low or absent in most elderly patients, due primarily to defects of iodine metabolism in tumoral tissues, and rhTSH is unlikely to provide clinical benefits in these patients.

In the extremely rare patients with metastases producing thyroid hormones, TSH level may remain low or suppressed even following thyroid hormone withdrawal. However, uptake of ^{131}I in these metastases is usually high enough to ensure delivery of an effective radiation dose to the neoplastic tissue. rhTSH may be of benefit by further increasing ^{131}I uptake. In general, following one treatment with ^{131}I , thyroid hormone production by the neoplastic tissue is reduced or abolished, and endogenous TSH level will increase following thyroid hormone withdrawal.

rhTSH for ablation

Another condition for which rhTSH is a promising alternative to prolonged thyroid hormone withdrawal is post-surgical ablation of thyroid remnants with ^{131}I , in the same way as bovine TSH was used in the past in this situation: rhTSH may be administered a few days

after surgery, or some weeks later while the patient is already receiving thyroid hormone treatment. However, in this situation the patient is euthyroid and dosimetric studies are needed to assess the amount of ^{131}I required to deliver an effective radiation dose to normal and neoplastic thyroid foci.

Conclusion

Clinical trials have clearly shown that rhTSH is an effective and safe alternative to thyroid hormone withdrawal for the follow-up of differentiated thyroid cancer. Both local and distant disease is adequately detected by rhTSH-stimulated Tg levels and, in most patients, sufficiently visualized by rhTSH-promoted ^{131}I -uptake. Although the intensity of stimulation seems to be lower with rhTSH than following thyroid hormone withdrawal, and the bioavailability of ^{131}I lower in euthyroidism (following rhTSH) than in hypothyroidism (following thyroid hormone withdrawal), the preservation of the quality of life offered by rhTSH largely overcomes these drawbacks.

Further studies and prospective clinical trials are still needed to answer some important clinical questions when using rhTSH, such as the most appropriate day for Tg testing, the advantages of Tg testing plus ^{131}I -TBS versus Tg testing alone, the optimal ^{131}I activity used for diagnosis and above all for therapy.

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