

Research Paper**The use of recombinant human thyrotropin (Thyrogen) in the diagnosis and treatment of thyroid cancer**

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ABSTRACT

The introduction of human recombinant thyrotropin (rhTSH/Thyrogen) into the diagnosis of thyroid cancer has substantially ameliorated the patient's quality of life through the avoidance of debilitating hypothyroidism. With the aim of updating the use of Thyrogen, we report 7 cases which were treated with Thyrogen for diagnostic or therapeutic purposes. All 7 patients were thyroidectomised and radioiodine ablated and all had detectable [> 1 ng/ml] basal serum thyroglobulin (b-Tg) levels. Thyrogen stimulation resulted in a rise of Tg (s-Tg) in all patients. Five patients had negative whole body scanning (WBS) and no clinical or radiological signs of disease. Two patients with a b-Tg value of 5 ng/ml and 11 ng/ml, respectively showed a s-Tg of 17 ng/ml and 84 ng/ml, respectively, whereas WBS was negative. Both of these patients received 100mCi (3700 MBq) ¹³¹I. Two patients had a positive Tg and positive WBS with skull, lung and hepatic metastases and received 150 ¹³¹I after preparation with Thyrogen. Six months later one of these patients was free of disease and the other will be evaluated during the coming months. In conclusion, Thyrogen emerges as a reliable and safe agent for the diagnosis of thyroid cancer. Furthermore, it appears that Thyrogen could be used in the treatment of metastases as an alternative to thyroid hormone withdrawal.

Key Words: human recombinant TSH, thyroglobulin, thyroid cancer, radiotherapy

INTRODUCTION

Over the last two decades a steady increase in the incidence of thyroid cancer has been observed¹. This may be due to a variety of environmental factors com-

bined with an increased awareness and better screening^{2,3}. Successful management of thyroid cancer is based on total thyroidectomy followed by radioiodine ablation and thyroxine therapy in TSH-suppressive doses. Long-term survival rate for well differentiated thyroid cancer is over 90%⁴. However, in 30% of patients tumor recurrence is observed, with 70% of these recurrences occurring within the first decade after therapy and the rest years later⁵. Thus, life-long follow-up is required to assess the prognosis of the tumor.

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Thyroglobulin (Tg) is produced exclusively by thyroid follicular cells and represents a sensitive marker for detection of local recurrence or thyroid cancer metastases after ablation⁶. It is noteworthy that the presence of anti-thyroglobulin antibodies, which have been reported in up to 25% of patients with thyroid cancer, may invalidate the significance of serum Tg measurement⁷. The performance of radioiodine scans requires the withdrawal of thyroid hormone therapy in order to achieve high TSH secretion⁸. However, the withdrawal of thyroid hormone results in severe hypothyroidism with such symptoms as extreme fatigue, depression, freezing sensation, and consequently, a markedly reduced quality of life (QOL)⁹. Recently, the introduction of recombinant human thyrotropin (rhTSH/ Thyrogen, Genzyme Corp., MA, USA) has significantly changed the procedure of follow-up evaluation of patients post thyroidectomy and radioiodine ablation^{10,11}. rhTSH is produced from human subunit genes transfected into Chinese hamster ovary cell lines¹². The administration of rhTSH for diagnostic whole-body scans and Tg measurement has proved comparable to thyroid hormone withdrawal in the detection of residual or recurrent thyroid cancer¹³. The use of rhTSH appears to be safe and reliably provides high concentrations of TSH while preserving the QOL of the patients by avoiding debilitating hypothyroidism¹¹.

We here report our experience with rhTSH in a small group of patients with well-differentiated thyroid cancer who were evaluated for residual or metastatic disease. The objective was to determine the diagnostic potency and safety of rhTSH. We further report the use of rhTSH as a therapeutic adjunct in two patients with metastatic disease.

MATERIALS AND METHODS

Patients

Seven patients (2 males, 5 females), mean age: 48yr (range: 38-57yr), were included in the study. Inclusion criteria were a detectable serum Tg (> 1 ng/ml) on thyroxine suppressive therapy and negative anti-Tg antibodies. All 7 patients had undergone a surgical thyroidectomy and radioiodine-131 ablation at least 12 months prior to the evaluation. Five of the patients had a papillary, one had follicular and one papillary-follicular thyroid carcinoma. Exclusion criteria were

the presence of anti-Tg antibodies, pregnancy or radioiodine treatment within the previous months.

Protocol

All patients received 0.9mg rhTSH by intramuscular injection on days 1 and 2. Five mCi of ¹³¹I were administered orally on day 3 and a WBS was performed on day 5. Determination of serum Tg and TSH were performed on day 1, prior to the first rhTSH injection, and on days 3 (n: 3) and 5.

Two out of the seven patients, who presented metastases at the liver, the sternum, the lung and the right frontal skull, were subsequently treated with radioiodine ¹³¹I after the administration of rhTSH for 2 consecutive days at the dose of 0.9 mg per day.

Measurements

Serum Tg levels were determined by IRMA (Byk-Sangtec, Dietzenbach, Germany) with a detection limit <0.075 ng/ml. The inter-assay coefficient of variation (CV) at 0.6 ng/ml was 9.1% and at 4 ng/ml was 2.9%, whereas the intra-assay CV at 0.39 ng/ml and at 4ng/ml was 10.5% and 2.2%, respectively. The normal range for Tg was 2-70 ng/ml. The functional sensitivity of the assay was calculated at 0.8 ng/ml and we arbitrarily selected 1 ng/ml as the cut-off level discriminating undetectable from detectable Tg levels.

TSH was measured by chemiluminescence with a TSH-3rd generation assay (Nichols, San Juan Capistrano, CA, USA). The normal values ranged from 0.3 to 4 mU/L. The mean intra-assay CV at 0.01 mU/L was 12% and at 1.29 mU/L was 4.6%. The inter-assay CV at 0.02 mU/L and at 1.28 mU/L was 15% and 5.5%, respectively.

RESULTS

Serum TSH levels peaked on day 3 at 127 ± 44 mU/L (mean \pm SD) and decreased to 14 ± 3.3 mU/L on day 5 (Figure 1).

All seven patients had a basal serum Tg (b-Tg) concentration above 1 ng/ml (Table 1). The response of Tg to Thyrogen was analogous to the basal level. Three patients with a b- Tg at 1.7 ng/ml, 2.2 ng/ml and 3.1 ng/ml, respectively, presented a rise after Thyrogen (s-Tg) of 3.3 ng/ml, 5 ng/ml and 7 ng/ml, respectively. In these patients the clinical evaluation and imaging studies like ultrasound (US), magnetic reso-

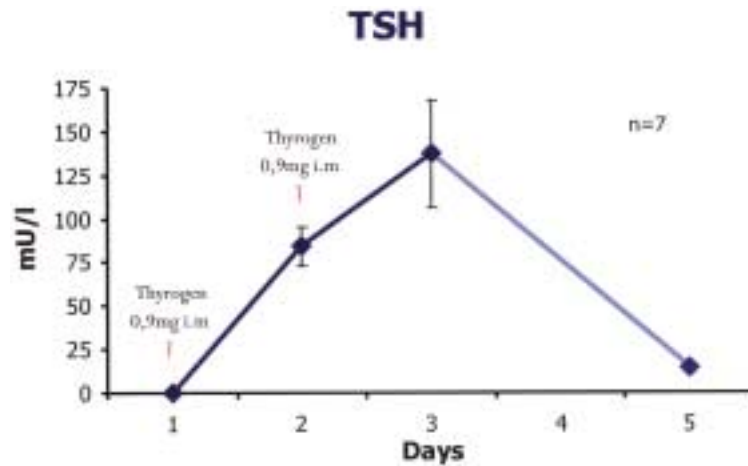


Figure 1. Basal and rhTSH stimulated serum TSH (mean ± SD) values in 7 patients with differentiated thyroid cancer.

nance (MRI) and WBS failed to detect metastatic lesion and only follow-up was recommended.

One out of the seven patients had a b-Tg value of 5 ng/ml and s-Tg of 17 ng/ml, whereas another had a b-Tg at 11 ng/ml and sTg at 84 ng/ml (Table 1). Both these patients had a negative WBS; they showed a comparable increase of serum Tg after withdrawal of thyroid hormone (hypo-Tg 19 ng/ml and 91 ng/ml, respectively). These two patients were treated with 100mCi (3700 MBq) ¹³¹I. Post-therapy scan was negative and a re-evaluation is planned in six months.

One patient, a 38-year old female, presented a b-Tg at 4.4 ng/ml, and a s-Tg of 78 ng/ml on day 3. The patient was thyroidectomised and radioiodine ablated in 1980 because of a mixed papillary-follicular carcinoma. She remained free of any recurrent disease for about 20 years. In the summer of 2002, b-Tg was found to be increased and metastases were detected

by L-thyroxine withdrawal, subsequent to which she was treated with 150mCi (5500 MBq) ¹³¹I. Thyrogen administration revealed a metastatic uptake at the posterior site of the liver, on the sternum and on the frontal skull (Figure 2). The patient was again treated with 150mCi ¹³¹I after preparation with rhTSH; Thyrogen was administered 0.9 mg intramuscularly each day, for the two days prior to the ¹³¹I administration.

Another patient, a 54-year-old female had a b-Tg of 16 ng/ml and an ¹³¹I metastatic uptake in the WBS after Thyrogen, at the apical lung field. She was also treated with 150 mCi ¹³¹I after preparation with Thyrogen. Six months after radioiodine treatment, b-Tg and s-Tg were <1 ng/ml and she had a negative WBS.

It should be noted that no patient had a visible radioiodine uptake in the thyroid bed, thus indicating

Table 1. Tg values prior to and after administration of Thyrogen

| No. Patients | Basal-Tg Day 1 (ng/ml) | Stimulated-Tg Day 3 (ng/ml) | Stimulated-Tg Day 5 (ng/ml) |
|--------------|------------------------|-----------------------------|-----------------------------|
| 1 | 1.7 | – | 3.3 |
| 2 | 2.2 | 6.3 | 5 |
| 3 | 3.1 | – | 7 |
| 4 | 5 | 15 | 17 |
| 5 | 11 | – | 84 |
| 6 | 4.4 | 78 | 81 |
| 7 | 16 | – | 77 |

–: not determined

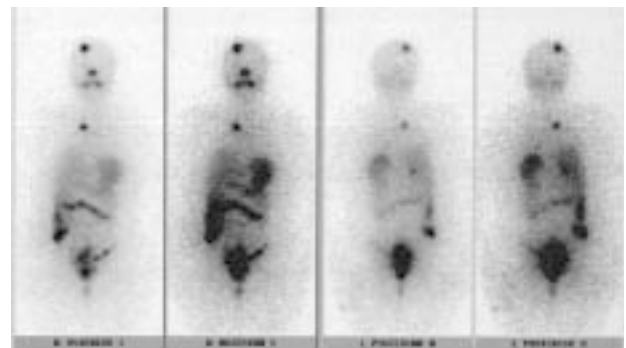


Figure 2. Anterior and posterior view of metastases on the frontal skull, the sternum and the liver, revealed by WBS, following rhTSH administration.

successful ablation. No side effects or complains were reported after Thyrogen administration.

DISCUSSION

The administration of rhTSH resulted in a variable increase of Tg in all 7 patients and revealed metastatic disease by WBS in two out of the seven patients.

Three patients had a slight increase of serum Tg levels and a negative WBS. They were not treated as Tg levels above 10 ng/ml are considered as a cut-off value for treatment of residual or recurrent thyroid cancer¹⁴. Two patients had rhTSH stimulated Tg levels (>10 ng/ml) with a negative WBS. No tumor was detected on radiological and US evaluation or by means of the traditional hypothyroid preparation WBS. They were consequently treated with doses of ¹³¹I, as normally used for ablation¹⁵. These data may indicate that rhTSH is useful in the management of patients with positive s-Tg and negative WBS (and negative US examination), specifically in distinguishing between patients who simply need a follow-up from those requiring therapeutic procedures. In the evaluation of these patients, rhTSH proved to be comparable to that after withdrawal of thyroid hormone, in accordance with recent reports^{16,13}.

In patients with increased serum Tg levels and negative ¹³¹I scans, a ¹⁸Fluoro-2-deoxy-D-glucose - positron emission tomography (FDG-PET) examination, may permit selection of patients for curative surgery¹⁷. Recently, it was demonstrated that TSH stimulates FDG uptake by differentiated thyroid cancer (DTC) and, therefore, FDG-PET may be more accurate under rhTSH than under suppression therapy¹⁸.

In parallel with the development of a simple Tg-stimulation test not requiring thyroid hormone withdrawal, such as the rhTSH test, the technical evolution of new assays for Tg with improved precision (<1 ng/ml) has certainly facilitated the diagnostic and therapeutic management of patients with DTC¹⁹.

In two of our seven patients, metastatic disease requiring further treatment was detected after thyroid hormone withdrawal as well as on rhTSH scan. These two patients were treated with ¹³¹I after preparation with Thyrogen. Both patients had suffered considerably in previous evaluations from the withdrawal

of thyroid hormone and therefore Thyrogen administration before treatment was considered as "compassionate use"^{20,21}. One of these two patients responded splendidly, being free of disease six months later. The other will be evaluated in a few months time.

There is no established protocol for using rhTSH to prepare the patient for ¹³¹I. These two patients are among the few who have been diagnosed by rhTSH and in whom rhTSH was subsequently administered to stimulate TSH secretion prior to radioiodine treatment. As both of our patients who received rhTSH prior to ¹³¹I therapy reported no side effects and the radioiodine by the metastatic lesions uptake was stimulated by rhTSH, we suggest that this treatment modality possibly constitutes a valid alternative to the classic therapeutic schedule requiring the interruption of L thyroxine. In a retrospective analysis of the use of rhTSH as preparation for radioiodine thyroid remnant ablation, it was reported that 84% of the patients prepared by rhTSH and 81% of those prepared by hormone withdrawal had complete resolution of visible thyroid bed uptake after ablation²². There are no prospective studies on the use of rhTSH as a treatment agent in patients with metastases due to thyroid cancer. In a case report, rhTSH was applied in a patient with thyroid cancer, primary empty sella and isolated deficiency of thyrotropin, in order to adequately stimulate the malignant tissue and optimize radioiodine uptake by the tumor cells²³.

The small number of patients in our report does not allow firm conclusions regarding future rhTSH assisted treatment. It is obvious that prospective and randomized studies are urgently needed. It is also noteworthy that serum peak TSH levels after rhTSH administration might be influenced by body size, and this may indicate that in future studies doses rhTSH should be adjusted to body size²⁴.

The detection of skull metastases by rhTSH in one of our patients may be added to other studies reporting the use of rhTSH for the diagnosis of metastases due to DTC. Thus, sella metastasis and hypopituitarism due to thyroid cancer were revealed by rhTSH²⁵. A highly functional metastatic struma ovarii from follicular thyroid carcinoma has recently been diagnosed and subsequently treated by rhTSH combined with lesional and whole body dosimetry²⁶. The wide use of rhTSH for diagnostic and potential therapeutic purposes in the future may significantly ameliorate the

QOL of thyroid cancer patients²⁷. In this context, rhTSH may be established as a safe and reliable agent improving the QOL of patients undergoing Tg testing and radioiodine scanning⁹.

The cost of rhTSH is not negligible. However, in the long term this cost may prove less than the indirect economic consequences on society of repeated episodes of hypothyroidism. In a study from the Netherlands, costs incurred through loss of productivity owing to hypothyroidism were estimated to be quite high²⁸. Thus, in order to reduce such negative repercussions on society, a comprehensive review of both the direct and indirect consequences of a therapeutic approach of this type is necessary to ascertain the most appropriate measures to be taken.

In conclusion, our results indicate that rhTSH is a reliable agent for the diagnosis of metastatic thyroid cancer disease, which increases the sensitivity of serum Tg testing, enhances iodine uptake and improves the QOL of patients with DTC. Moreover, it may represent a valuable agent for the preparation of patients for radioiodine treatment.

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