Expanding use of recombinant hTSH

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Available online 08 August 2007

Abstract

The clinical benefits of recombinant human thyroid-stimulating hormone (rhTSH; Thyrogen®, Genzyme Corp., Cambridge, MA, USA) are well established as an alternative stimulation procedure to thyroid hormone withdrawal in the follow-up of thyroid cancer patients. rhTSH has the advantage to avoid both hypothyroidism, with a major impact on the quality of life, and the side effects on tumor growth related to the long-lasting TSH increase. More recently, alternative uses have been proposed, including treatment of nodular goiter, TSH stimulation to enhance PET scanning and chemotherapy treatment, and differential diagnosis of congenital hypothyroidism. In benign thyroid diseases, rhTSH administration increases thyroid uptake resulting in a more homogeneous distribution of the tracer, and allows to reduce the dose of 131I maintaining the same effects on thyroid shrinkage. Moreover, rTSH stimulation improves the detectability of occult thyroid metastases with FDG-PET, and promising results have been obtained in the response rate of poorly differentiated thyroid cancer submitted to chemotherapy after rhTSH stimulation. Finally, rhTSH testing has been proved to be safe and to lead, in association with ultrasound, to the differential diagnosis of congenital hypothyroidism during L-thyroxine, allowing the appropriate clinical/genetic management of the disease and thus representing a valuable alternative to L-thyroxine withdrawal.

1. Introduction

The clinical benefits of recombinant human thyroid-stimulating hormone (rhTSH; Thyrogen®, Genzyme Corp., Cambridge, MA, USA) are well established as an alternative stimulation procedure to thyroid hormone withdrawal in the follow-up of thyroid cancer patients. Indeed, it has been demonstrated that rhTSH administration (0.9 mg/die in following 2 days) is effective in the stimulation of 131I uptake and thyroglobulin (Tg) production by normal residual tissue, local relapse or metastases and comparable to thyroxine withdrawal [4,7,9,14]. Main advantages of rhTSH are the higher reliability of the diagnostic investigations and the possibility to avoid periods of hypothyroidism. Consequently, patients do not suffer from a decreased quality of life and keep their ability to work. More recently, successful thyroid ablation has been reported after rhTSH preparation using 131I activity determined by individual dosimetry [15], or after a fixed dose of 3700 MBq [12]. The latter procedure has been approved in 2005 in Europe for the preparation to the administration of 131I to low-risk patients. When using rhTSH for thyroid ablation, the patient should receive one i.m. injection of 0.9 mg rhTSH on consecutive 2 days and receive radioiodine 24 h after the second injection. Finally, though not yet approved for this purpose, rhTSH has been successfully used in a compassionate use program for the preparation to 131I therapy of patients with distant metastases [8]. Although the majority of the literature regarding the diagnostic uses of rhTSH relates to thyroid cancer detection and treatment, alternative uses have been proposed, including treatment of nodular goiter, TSH stimulation to enhance PET scanning and chemotherapy treatment, and differential diagnosis of congenital hypothyroidism.

2. RhTSH in the radiometabolic treatment of non-toxic nodular goiter

Patients with large non-toxic nodular goiters (MNG) frequently suffer with symptoms of neck compression. These symptoms can include dysphagia, odynophagia and sensations of throat compression. Additionally, these patients can have
extrathoracic airway obstruction resulting in impaired airflow. Although treatment of these large, compressive non-toxic nodular goiters is usually accomplished by surgical resection, radioiodine has been used to reduce goiter volume, particularly in patients who are poor surgical candidates due to other comorbid conditions. In the last 15 years, a growing interest in \(^{131}\)I treatment of MNG has been recorded. Several studies demonstrated that \(^{131}\)I treatment is followed by a significant and permanent thyroid volume reduction (typically 50–60% reduction at 2–5 years) and improvement of obstructive symptoms \([5,6,11,19,20]\). Nontoxic nodular goiters usually have relatively low radioiodine uptake values and high treatment doses of \(^{131}\)I are often required to induce substantial goiter size reduction. Pretreatment of patients with rhTSH may enhance radioiodine uptake and improve efficacy of \(^{131}\)I to reduce goiter volume. Different doses of rhTSH have been used to this purpose, ranging from very low doses (0.01 and 0.03 mg, \([10]\)) up to higher doses (0.45 mg, \([17]\)). In all cases, two or more folds increased thyroid uptake and a more homogeneous uptake was observed. Moreover, it has been demonstrated that the administration of rhTSH before radiiodine treatment allows reducing the dose of \(^{131}\)I to be administered, without compromise of efficacy \([10]\).

Alterations in thyroid function constitute the main side effects of \(^{131}\)I treatment. In particular, transient thyrotoxicosis has a prevalence varying between 3 and 27%, while hypothyroidism has been reported after a follow-up of 1–2 years in 21–48% of treated patients, depending on the dose of \(^{131}\)I employed and on the thyroidal uptake \([5,6,11,19,20]\). In this context, a major disadvantage of the pretreatment with rhTSH is the high prevalence of \(^{131}\)I-induced hypothyroidism. Indeed, while radioiodine induced hypothyroidism is observed in 10–20% of patients treated with \(^{131}\)I alone \([19]\), the percentage rises to 36–65% in patients pre-treated with rhTSH \([10,17]\).

3. TSH stimulation to enhance PET scanning and chemotherapy treatment

\(^{18}\)Fluoro-2-deoxyglucose (FDG) PET scanning has been shown to be useful in patients with thyroid carcinoma, elevated Tg levels and negative \(^{131}\)I Total Body Scan. Since the sensitivity of diagnostic techniques such as Tg determination and iodine concentration is enhanced by TSH stimulation, some Authors hypothesized that TSH would also increase FDG uptake by increasing glucose transport and/or glycolytic activity, in thyroid cancer patients \([1,13]\). With this aim, stimulated scans were performed after two 0.9 mg i.m. doses of rhTSH, while patients continued the same L-thyroxine dose. The results were encouraging since all lesions seen on the basal scans during TSH suppression were also visualized on the rhTSH stimulation studies. Moreover, after rhTSH stimulation additional lesions, not seen on TSH suppression, were identified and, in a minority of cases, PET was positive on rhTSH stimulation alone. The mean and maximum lesions to background ratios were significantly higher with rhTSH stimulation, compared with TSH suppression. Interestingly, no correlation was observed between the appearance of additional foci on rhTSH-stimulated PET scans and the difference between basal and rhTSH-stimulated thyroglobulin levels. Authors concluded that rhTSH-stimulation improves the detectability of occult thyroid metastases with FDG-PET, compared with scans performed on TSH suppression, suggesting a potential role for rhTSH-stimulated FDG-PET scanning in the detection of persistent disease.

The rationale for the use of rhTSH in chemotherapy is to evaluate whether increasing the metabolic rate of thyroid cancer cells by TSH stimulation might result in higher response rate to chemotherapy in patients with poorly differentiated thyroid carcinoma and non-functioning metastases detected at computed tomography scan. In a study by Santini and coworkers \([16]\) a combination of carboplatinum and epirubicin was administered and TSH stimulation achieved either by reduction of the daily dose of L-thyroxine resulting in mild hypothyroidism or by administration of rhTSH. At each course, patients received 1 injection of 0.9 mg rhTSH for consecutive 2 days and chemotherapy was administered on day 3. The overall rate of positive responses was 37% that rose to 81% when including patients with stable disease. Serum Tg after chemotherapy declined more than 50% in about half of patients, with respect to basal levels. Apparently, no difference in the response rate was observed between exogenous or endogenous TSH stimulation. After 21 months of chemotherapy, 64.3% were still alive, most of them showing a stable disease. Authors concluded that the response rate of poorly differentiated thyroid cancer to chemotherapy after rhTSH stimulation was favorable and promising.

4. RhTSH in the differential diagnosis of congenital hypothyroidism

Another important application of rhTSH is the differential diagnosis of congenital hypothyroidism (CH) (Table 1). The differential diagnosis of CH is mainly aimed to distinguish between transient and permanent hypothyroidism in order to avoid unnecessary prolongation of treatment and psychosocial problems due to continuous monitoring. On the other hand, an

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Diagnostic and therapeutic uses of recombinant human TSH (Thyrogen®, Genzyme Corp., Cambridge, MA, USA). The dosage (i.m. administration) required for each use is also reported</th>
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<tr>
<td>Diagnoctic</td>
<td>Dose</td>
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<td>Evaluation of stimulated Tg with or without TBS in the follow-up of differentiated thyroid cancer; in alternative to THW</td>
<td>0.9 mg × 2 days</td>
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<td>Differentiated thyroid cancer (central hypothyroidism)</td>
<td>0.9 mg × 2 days</td>
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<tr>
<td>FDG-PET</td>
<td>0.9 mg × 2 days</td>
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<tr>
<td>Differential diagnosis of CH</td>
<td>0.004 mg/kg × 2 days or × 3 days</td>
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<tr>
<td>Therapeutic</td>
<td>Dose</td>
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<tr>
<td>Remnant ablation</td>
<td>0.9 mg × 2 days</td>
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<tr>
<td>Treatment of thyroid cancer metastases; in alternative to THW; compassionate programme</td>
<td>0.9 mg × 2 days</td>
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<tr>
<td>Non-toxic nodular goiter</td>
<td>0.45 mg or 0.01 mg or 0.03 mg × 1 day</td>
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<tr>
<td>Enhancement chemotherapy</td>
<td>0.9 mg × 2 days</td>
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<td>THW: thyroid hormone withdrawal.</td>
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Fig. 1. The proposed protocols for the differential diagnosis of congenital hypothyroidism by rhTSH testing during L-thyroxine replacement treatment, according to the ultrasonographic diagnosis at enrolment.

Accurate definition of the defect is required to undertake appropriate genetic investigations and family counseling. The etiologic diagnosis of CH is based on clinical examination, biochemical tests, thyroid ultrasound and scintigraphy (99mTc, 131I) or preferably 123I uptake with or without perchlorate discharge test). A complete clinical evaluation, and in particular thyroid scintigraphy and discharge test, can be performed before the early start of L-thyroxine in neonates only in specialized centers. In other settings, due to the lack of adequate facilities for the management of these neonates, these examinations are postponed during infancy in order to allow early therapy. Thus, tests are completed at 2–4 years of age, after 1 month of L-thyroxine withdrawal [18]. The resulting hypothyroid state is associated with particular concern by several parents and with untoward effects including rapid and great thyroid enlargement if the underlying CH cause is defective hormonogenesis. With the aim to verify the efficacy and safety of new protocols for rhTSH testing in the etiologic diagnosis of CH during L-thyroxine replacement, we tested new protocols in an pilot group of adult patients [2] and more recently in a cohort of pediatric patients (age range 15–144 months) with different forms of CH [3]. All patients remained on L-thyroxine therapy and underwent new protocols for rhTSH testing. In the first study on adult patients, a standard protocol was used with the administration of 4 μg/kg per day of rhTSH during 3 days and thyroid scintiscan on days 3 and 4. At variance, in the study on pediatric patients, children underwent distinct rhTSH protocols depending upon the CH classification of the defect made at birth (Fig. 1). Patients with ultrasonographic diagnosis of gland in situ underwent 2 rhTSH injections (4 μg/kg per day, i.m.) on days 1 and 2. A thyroid scintigraphy with 123I and a perchlorate discharge test were performed on day 3. In particular, 123I was administered intravenously and counts were obtained at 1 and 2 h. For the discharge test, 200 or 400 mg of potassium perchlorate were administered orally and uptake was calculated after 1, 2 and 3 h. In the patients with hæmagenesis or apparent agenesis at the ultrasonography examination performed at enrolment, 3 rhTSH injection were given on days 1–3 in order to enhance testing sensitivity for the disclosure of small tissue remnants. On day 3, 123I was given (9.25 MBq) and head, neck and mediastinum uptakes were measured after 2 and 24 h. In order to make the most of each rhTSH vial, patients were divided in groups and each vial reconstituted in 4 ml sterile water.

After rhTSH injections, TSH levels peaked 33.5–68.2 mU/l on day 4 in the “adult study” and to 10.9–59.2 mU/l, on days 3 or 4 in the “children study”. Free thyroid hormones levels were always in the normal range and anti-thyroid autoantibodies were negative in all cases.

Thyroglobulin peaks varied according to the diagnosis. Indeed, a mean of 3-folds elevation was observed in patients with a final diagnosis of total iodide organization defect (TIOD), while blunted Tg responses were observed in cases with a final diagnosis of agenesis or resistance to TSH action. Interestingly, extremely variable Tg responses were observed in the cases of ectopy, ranging from very mild elevations up to 15-folds increases. Nevertheless, the present rhTSH testing protocols have been proved to stimulate thyroid uptake and to cause Tg increases even in the presence of minimal amounts of responsive thyroid cells that could not be visualized at scintiscan or ultrasound. All protocols for rhTSH testing allowed the accurate definition of the underlying defect in each patient, providing useful information about the defective step in thyroid development or function in all the patients. In particular, considering the adult and pediatric patients studied, the accuracy of rhTSH testing was demonstrated in a considerable number of patients for the different CH categories (7 with ectopia, 3 with agenesis, 3 with TIOD, 4 with TSH resistance and 3 transient forms). Testing by rhTSH is particularly useful in patients with the clinical suspicion of a dysmormogenic defects. Indeed, the discontinuation of L-thyroxine needed to perform the discharge test is not recommended since hypothyroidism can induce a dramatic thyroid enlargement in these cases. Moreover, rhTSH test may be performed very early in postnatal life, thus allowing the selection of candidates for L-thyroxine withdrawal. This would finally prevent the unnecessary prolongation of replacement treatment in transient CH.

Thanks to the accurate classification of the disorder; targeted genetic analyses could be performed in many patients, leading to the identification of TPO mutations in three cases. As far as the cost benefit analysis of the present protocols is concerned, it must be underlined that the doses of rhTSH used are extremely low. Indeed, the dose for the differential diagnosis in one CH patient is 6-folds lower than that used to test one patient with thyroid cancer. This is obviously possible only by appropriate grouping of patients.

In conclusion, emerging uses for recombinant human TSH have been reported. In the diagnosis and treatment of thyroid cancer, rhTSH has the advantage to avoid both hypothyroidism, with a major impact on the quality of life, and the side effects on tumor growth related to the long-lasting TSH increase. In benign thyroid diseases, rhTSH administration increases thyroid uptake resulting in a more homogeneous distribution of the tracer, and allows reducing the dose of 131I maintaining the same effects on thyroid shrinkage. Finally, rhTSH testing has been proved to be safe and to lead, in association with ultrasound, to the differential diagnosis of congenital hypothyroidism during L-thyroxine, allowing the appro-
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References


