Recombinant Human Thyrotropin as an **Adjuvant** to **Radioiodine Therapy** for **Nontoxic, Nodular Goiter**

Willy-Anne Nieuwlaat

Recombinant Human Thyrotropin as an **Adjuvant** to **Radioiodine Therapy** for **Nontoxic, Nodular Goiter**

Recombinant Human Thyrotropin as an **Adjuvant** to **Radioiodine Therapy** for **Nontoxic, Nodular Goiter**

Willy-Anne Nieuwlaat

Nieuwlaat, Wilhelmina A.C.M.

Recombinant Human Thyrotropin as an Adjuvant to Radioiodine Therapy for Nontoxic, Nodular Goiter
Dissertation Radboud University Nijmegen, with summary in Dutch

ISBN 90-9019225-5

Design & production: Macx Reclamestudio, Nijmegen, The Netherlands
Cover illustration © by Genzyme Corporation, Cambridge MA, United States of America

The studies described in this dissertation were performed at the Department of Nuclear Medicine, Catharina Hospital, Eindhoven and the Departments of Endocrinology and Nuclear Medicine, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

Recombinant Human Thyrotropin as an **Adjuvant** to **Radioiodine Therapy** for **Nontoxic, Nodular Goiter**

Een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de Rector Magnificus prof. dr. C.W.P.M. Blom,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op vrijdag 13 mei 2005
des namiddags om 1.30 uur precies

door

Wilhelmina Anna Cornelia Maria Nieuwlaat
geboren op 25 oktober 1969 te Roosendaal

Promotores:	Prof. dr. A.R.M.M. Hermus Prof. dr. F.H.M. Corstens
Co-Promotor:	Dr. D.A.K.C. Huysmans
Manuscriptcommissie:	Prof. dr. A.F.H. Stalenhoef, voorzitter Prof. dr. W.M. Wiersinga (Universiteit van Amsterdam) Dr. J.M.H. de Klerk (Universiteit Utrecht)

Recombinant Human Thyrotropin as an **Adjuvant** to **Radioiodine Therapy** for **Nontoxic, Nodular Goiter**

A scientific essay in the Medical Sciences

Doctoral Thesis

to obtain the degree of doctor of philosophy
from the Radboud University Nijmegen
on the authority of Rector Magnificus prof. dr. C.W.P.M. Blom,
according to the decision of the Council of Deans
to be defended in public on Friday May 13, 2005
at 1.30 pm

by

Wilhelmina Anna Cornelia Maria Nieuwlaat
born in Roosendaal, The Netherlands on October 25, 1969

Doctoral Supervisors:	Prof. dr. A.R.M.M. Hermus Prof. dr. F.H.M. Corstens
Co-Supervisor:	Dr. D.A.K.C. Huysmans
Doctoral Thesis Committee:	Prof. dr. A.F.H. Stalenhoef, chair Prof. dr. W.M. Wiersinga (University of Amsterdam) Dr. J.M.H. de Klerk (University Utrecht)

The publication of this dissertation was supported by
Genzyme Corporation, Naarden, The Netherlands.

“The Butterfly Effect”

Predictability: Does the Flap of a Butterfly’s Wings in Brazil Set off a Tornado in Texas?

Edward N. Lorenz, The Essence of Chaos
1996, Seattle WA, University of Washington Press

contents

Chapter 1 15

General Introduction and Outline of the Thesis

1.1 Nontoxic, Nodular Goiter 17
Published in part as Nontoxic, Nodular Goiter: New Management Paradigms
The Endocrinologist 2003; 13(1):31-37

1.2 Thyrotropin (TSH) 27

1.3 Bovine and Human Cadaver Pituitary TSH 31

1.4 Recombinant Human Thyrotropin (rhTSH) 35

1.5 Outline of the Thesis 55

Chapter 2 69

2.1 Administration of a Single Low Dose of Recombinant Human Thyrotropin Significantly Enhances Thyroid Radioiodide Uptake in Nontoxic Nodular Goiter 71
The Journal of Clinical Endocrinology & Metabolism 2000; 85(10):3592-3596

2.2 Addendum 85

Chapter 3 89

3.1 Pretreatment with Recombinant Human TSH Changes the Regional Distribution of Radioiodine on Thyroid Scintigrams of Nodular Goiters 91
The Journal of Clinical Endocrinology & Metabolism 2001; 86(11):5330-5336

Chapter 4 **109**

4.1 Pretreatment with a Single, Low Dose of Recombinant Human Thyrotropin Allows Dose Reduction of Radioiodine Therapy in Patients with Nodular Goiter 111
The Journal of Clinical Endocrinology & Metabolism 2003; 88(7):3121-3129

4.2 Letter to the Editor and Authors' Response: Pretreatment with a Single, Low Dose of Recombinant Human Thyrotropin Allows Dose Reduction of Radioiodine Therapy in Patients with Nodular Goiter 129
The Journal of Clinical Endocrinology & Metabolism 2003; 88(12):6113-6115

Chapter 5 **137**

5.1 Dosimetry of Radioiodine Therapy in Patients with Nodular Goiter After Pretreatment with a Single, Low Dose of Recombinant Human Thyroid-Stimulating Hormone 139
The Journal of Nuclear Medicine 2004; 45(4):626-633

Chapter 6 **159**

6.1 Summary 161
6.2 Perspective 167
Published in part as Towards Larger Volume Reduction of Nodular Goitres by Radioiodine Therapy: a Role for Pretreatment with Recombinant Human Thyrotropin?
Clinical Endocrinology 2004; 60(3):297-299

Chapter 7 **177**

7.1 Samenvatting 179
7.2 Perspectief 185

Chapter 8 **197**

8.1 Dankwoord 199
8.2 Curriculum Vitae 203
8.3 List of Publications 207

chapter

1

1.1

Nontoxic, Nodular Goiter

Willy-Anne Nieuwlaat, Ad R. Hermus,
and Dyde A. Huysmans

Department of Nuclear Medicine (W.-A.N., D.A.H.),
Catharina Hospital, Eindhoven;
Department of Endocrinology (W.-A.N., A.R.H.),
Radboud University Nijmegen Medical Center, Nijmegen,
The Netherlands

Published in part as
Nontoxic, Nodular Goiter: New Management Paradigms
The Endocrinologist 2003; 13(1): 31-37

1.1

In this thesis the use of recombinant human thyrotropin (rhTSH) as a possible adjunct to radioiodine therapy for thyroid volume reduction in patients with nontoxic, nodular goiter is explored. This first chapter reviews the clinical manifestations, diagnostic evaluation and treatment (by thyroidectomy, L-thyroxine or radioiodine) of nontoxic, nodular goiter. Next, an introduction to the hormone thyrotropin (thyroid stimulating hormone, TSH) is given and thereafter we focus on the development of rhTSH for use in humans, particularly in patients with differentiated thyroid cancer.

Nontoxic, Nodular Goiter

1.1.1 Introduction

Nontoxic, nodular goiter may be defined as a structurally and functionally heterogeneous thyroid enlargement in an euthyroid patient, which is not caused by an autoimmune, inflammatory or neoplastic process. Worldwide, the most frequent cause of goiter is iodine deficiency. In nonendemic areas the etiology of goiter is multifactorial with a hereditary predisposition and a female preponderance. The initially diffuse goiters tend to grow gradually and to become more nodular. This can lead to compression of the trachea and esophagus and obstruction of venous outflow. With time, thyroid function often becomes more autonomous (1), and euthyroidism may gradually change into subclinical and eventually into overt hyperthyroidism.

1.1.2 Clinical manifestations

A nontoxic goiter is often discovered incidentally in an asymptomatic patient. The clinical manifestations of nontoxic, nodular goiter are caused by compression of vital structures in the neck or upper thoracic cavity (trachea, esophagus, and neck veins). Patients with mild tracheal compression are usually asymptomatic. When tracheal narrowing becomes more severe, dyspnea and stridor develop, initially only on exertion, but later also at rest. In patients with intrathoracic extension of a goiter, dyspnea, and stridor may be nocturnal or positional, occurring especially during maneuvers that force the thyroid into the thoracic inlet, like reaching. Esophageal compression is less common than tracheal compression because the esophagus is positioned more posteriorly in the neck. Obstruction of the jugular or subclavian veins or the superior vena cava results in facial plethora and dilated neck and upper thoracic veins. Vocal cord paralysis, either transient or permanent, can occur because of stretching or compression of a recurrent laryngeal nerve and results in hoarseness and dyspnea.

1.1.3 Diagnostic evaluation

The diagnostic evaluation of a patient with a nontoxic, nodular goiter starts with a careful history and physical examination. Serum TSH and free thyroxine levels should be measured to identify (subclinical) hyperthyroidism. Thyroid scintigraphy and ultrasonography are not routinely indicated. Patients who have symptoms and signs of tracheal compression (inspiratory stridor and dyspnea) should have radiographs taken of the trachea or CT or MR imaging of the neck and upper thorax. Iodinated contrast agents should be avoided because of the risk of inducing hyperthyroidism. Pulmonary function tests, especially flow-volume loops, are useful to evaluate airway obstruction. Fine-needle aspiration biopsy may be helpful when thyroid cancer is suspected. Cytology should be obtained from dominant nodules and those with a firmer consistency within the thyroid gland (2).

1.1.4 Treatment

The main indications for treatment of patients with nontoxic, nodular goiter are compression of the trachea or esophagus and venous outflow obstruction. Other indications are goiter growth, neck discomfort, and cosmetic concerns. There are three treatment options: thyroidectomy, suppression therapy with L-thyroxine and administration of radioactive iodine. These will be discussed here.

1.1.4.1 Thyroidectomy

Surgery is standard therapy for patients with nontoxic, nodular goiter. Surgical treatment, usually consisting of bilateral subtotal thyroidectomy, leads to fast decompression of vital structures. A second advantage of surgical treatment is the possibility of histopathological examination of the removed tissue.

Resection of goiters, even of substernal ones, can usually be accomplished through a transcervical approach, either by digital mobilization or by using a spoon technique (3). Therefore, thoracotomy is rarely needed. However, surgical treatment is not without risk. Surgical morbidity (vocal cord paralysis, hypoparathyroidism, tracheal obstruction caused by tracheomalacia, and hemorrhage) is higher in patients with large goiters and in case of subsequent operations. The rate of postoperative hypothyroidism depends on the extent of surgery. The mortality for bilateral thyroid operations in nontoxic, nodular goiter is less than 1 percent.

The rate of goiter recurrence increases with the duration of follow-up after surgery. With adequate surgery, the recurrence rate should not be higher than approximately 10% after 10 years. Postoperatively, L-thyroxine is frequently prescribed to decrease the chance of goiter recurrence. However, several studies have yielded no convincing evidence that this treatment is effective (4,5).

1.1.4.2 L-Thyroxine

Thyroid hormone therapy is the second treatment option for patients with nontoxic, nodular goiter. The hypothesis underlying L-thyroxine treatment is that growth of a nontoxic, nodular goiter, like that of normal thyroid tissue, is dependent on TSH secretion and therefore, that suppression of TSH secretion will cause shrinkage of the goiter.

Only two randomized trials on the effect of L-thyroxine therapy in patients with nontoxic goiter using objective thyroid volume measurements have been reported. In a study by Berghout et al. (6) thyroid volume decreased significantly after 9 months of L-thyroxine treatment in TSH-suppressive doses in about half of the patients (mean decrease 25% in the responders). Goiter size returned to baseline after discontinuation of therapy. In a recent study by Wesche et al. (7) a significant decrease in goiter size was observed in 43% of patients after 2 years of L-thyroxine therapy (mean decrease 22% in the responders). In the nonresponders a mean increase in thyroid volume of 16% was found.

The efficacy of L-thyroxine treatment in patients with large, nodular goiters is probably even less than found in the above mentioned randomized studies in which most patients had relatively small goiters. Many patients with large nodular goiters have a serum TSH level below the normal range, and no shrinkage of the goiter can be expected when TSH secretion is already suppressed (8). Furthermore, L-thyroxine therapy is inadvisable in patients with a suppressed serum TSH level, because it may cause overt thyrotoxicosis.

There is no evidence that L-thyroxine therapy alters the natural history of nodular goiter. Therefore, lifelong treatment is probably necessary. Long-term treatment with L-thyroxine in doses sufficient to suppress serum TSH may have adverse effects on bone mineral density and on the heart. A meta-analysis, comprising all controlled cross-sectional studies on the effects of L-thyroxine therapy on bone mineral density published between 1982 and 1994, demonstrated significant decreases in bone mineral density at the lumbar spine, the proximal femur, and the radius in postmenopausal women receiving long-term thyroid hormone suppression therapy (9). No negative effect of therapy on bone mineral density was found in premenopausal women and in men. In contrast, a recent longitudinal study showed also in premenopausal women a decrease in bone mineral density after only 2 years of suppression therapy with L-thyroxine (7).

A low serum TSH concentration in persons 60 years of age or older is associated with a threefold increased risk of developing atrial fibrillation in the subsequent decade (10). Therefore, it is not unreasonable to assume that thyroid hormone suppression therapy might have cardiac adverse effects. This therapy does indeed increase left ventricular mass. Whether it also causes cardiac dysfunction is not clear. Studies on this subject have yielded discordant results (11-13).

1.1.4.3 Radioiodine

In the first studies on radioiodine therapy for nontoxic goiter, which appeared in the German literature, satisfactory clinical results with response rates ranging from 65% to 99% were reported in large numbers of patients (14-16). Several years later, two retrospective studies were published in the Anglo-Saxon literature, comprising 14 and 15 patients, respectively (17,18). Response rates in these studies were fairly high (79% and 100%, respectively). In these early studies the effects of radioiodine therapy were evaluated by measurements of neck circumference and by thyroid volume measurements using palpation and planar scintigraphy, methods that are known to be inaccurate.

In later studies, comprising a total of 252 patients, accurate measurements of thyroid volume were performed by ultrasonography, CT and MRI (Table 1). Ultrasound was used in the studies on relatively small nodular goiters (mean thyroid volumes varying from 56 to 88 mL), whereas MRI and CT were used in the studies on large nodular goiters (mean thyroid volumes varying from 194 to 311 mL).

Radioiodine treatment resulted in a mean reduction in thyroid volume of approximately 40% after 1 year (7,19-24). A positive correlation between the reduction in goiter volume and the dose of radioiodine per gram of thyroid tissue was found (23,25), and a negative correlation between the decrease in goiter volume and pretreatment goiter volume (7,25). Furthermore, the degree of nodularity of the goiter appeared to influence the result of radioiodine therapy. In a study by Hegedüs et al. (26) on nontoxic, diffuse goiters thyroid volume reduction was 60% on average at one year after radioiodine therapy, which is considerably larger than the above mentioned 40% found in studies on nontoxic, nodular goiters.

In most studies, iodine-131 doses were aimed at an absorbed dose of 3.7 to 4.4 MBq (100 to 120 μCi) iodine-131 per gram of thyroid tissue, corrected for the percentage uptake of radioiodine in the thyroid at 24 hours. Standard, fractionated doses may also be effective (27). However, studies on this issue with accurate measurements of thyroid volume are lacking.

In most patients not only thyroid volume but also compressive symptoms decreased. In one study, there was a significant tracheal widening as measured by MRI (21) (Figure 1), and improvement in respiratory function was found in two studies (21,28).

Long-term results of radioiodine treatment for nontoxic, nodular goiter are also satisfying. Decreases in thyroid volume of 50% to 60% after 3 to 5 years have been reported (20,25,29). In the study by Nygaard et al. (20) it was observed that thyroid volume decreased during the first 2 years after radioiodine treatment (Figure 2). Thereafter no significant further changes were observed.

Early side effects (pain in the thyroid region, radiation thyroiditis, increase in compression symptoms, esophagitis) were usually mild and transient (21,29,30). In studies on the effects of radioiodine therapy on thyroid volume and thyroid hormone levels in the first weeks after therapy only small increases in thyroid volume and serum thyroid hormone levels were found (24,30). The development of autoimmune (Graves') hyperthyroidism is the most important late complication, occurring several months after therapy. It is probably triggered by radiation-induced release of thyroid antigens, and elevated serum levels of TSH receptor antibodies have been found at the time of thyrotoxicosis (31,32). The incidence of this complication is approximately 5%. The hyperthyroidism may be quite severe. Therefore, informing patients to be alert on symptoms and signs of hyperthyroidism is important to promptly recognize this complication.

Reported incidences of posttreatment hypothyroidism after radioiodine therapy for nontoxic, nodular goiter in literature vary from 8% to 100% (7,18-20,22-25). Nygaard and coworkers (20), using the life table method, calculated a cumulative risk of hypothyroidism of 22% at 5 years after radioiodine treatment for small nontoxic goiters. However, in more recent studies higher incidences were found, e.g., 22% after 1 year (24) and 45% after 2 years (7). Posttreatment hypothyroidism appears to be more common in patients with small goiters and in those with high pretreatment serum antithyroid peroxidase antibody concentrations (25).

An important issue is the risk of induction of cancer by radioiodine therapy for volume reduction of nontoxic, nodular goiters, because large doses of radioiodine are used, especially for large goiters with low radioiodine uptake. There are no follow-up data on cancer incidence in patients with nontoxic, nodular goiter treated with radioiodine. The risk for induction of thyroid cancer is not higher than that after radioiodine therapy of patients with small, toxic nodular goiters, because the absorbed doses in the thyroid are similar. The lifetime risk of radiation-induced cancer in extrathyroidal tissues and organs strongly depends on the administered dose of radioiodine and on the age of the patients. It has been estimated that the lifetime risk of radiation-induced cancer in extrathyroidal tissues in people of 65 years and older, treated with high doses of radioiodine, is similar to the surgical mortality of subtotal thyroidectomy (33).

Until now, most clinicians have restricted radioiodine therapy for nontoxic goiter to elderly patients, especially those who have a high operative risk or refuse surgery. In these patients, the benefit of noninvasive radioiodine treatment outweighs the lifetime risk of radiation-induced cancer. However, radioiodine may prove to be an attractive alternative to surgery in younger patients, provided that the dose of radioiodine administered is relatively low (e.g., patients with small goiters and sufficient radioiodine uptake).

In this respect, it is of interest to explore strategies to enhance radioiodine uptake in patients with nontoxic, nodular goiter. One of the causes of a low uptake in patients with nontoxic, nodular goiter is the fact that the serum TSH level is in the low-normal range or even below normal in most of these patients. Therefore, the administration of thyrotropin before radioiodine therapy for nontoxic goiter can be expected to increase the uptake of radioiodine in the thyroid.

Table 1. *Data in the literature on the efficacy and side effects of radioiodine therapy for nontoxic, nodular goiter. Summary of studies, using objective methods for thyroid volume measurements.*

		Number of patients	Method used for volume measurement[a]	Goiter Size[b] (mL)	^{131}I dose Aimed (μCi/g)	^{131}I dose Administered[b] (mCi)	Follow-up (years)	Volume Reduction[b]	Reported Side Effects[c]		
									Thyroiditis	Hyperthyroidism	Hypothyroidism
Hegedüs L, et al.	1988	25	US	73	100	15 (7-28)	1	41%	none	1/25 (4%)	2/25 (8%)
Nygaard B, et al.	1993	69	US	74 (21-296)	100	15 (4-30)	5 (1-10)[b]	55%	2/69 (3%)	3/69 (4%)	11/69 (16%)
Huysmans DA, et al.	1994	19	MRI	269 (109-825)	100	71 (37-150)	1	40 (19-68)%	2/19 (11%)	1/19 (5%)	n.m.
Wesche MF, et al.	1995	10	US	88	120	20 (14-65)	1	48 (27-73)%	1/10 (10%)	none	4/10 (40%)
de Klerk JM, et al.	1997	27	CT	194 (42-491)	90	35 (14-100)	1	34 (3-65)%	none	none	3/21 (14%)
Le Moli R, et al.	1999	50	US	82 (17-325)	100	27 (12-90)	2	49%	n.m.	n.m.	24/50 (48%)
Bonnema SJ, et al.	1999	23	MRI	311 (100-703)	150	62 (27-125)	1	34 (14-61)%	none	none	5/23 (22%)
Wesche MF, et al.	2001	29	US	56 (17-198)	120	24 (12-90)	2	44 (6-84)%	4/29 (14%)	none	13/29 (45%)

[a] US = ultrasound; MRI = magnetic resonance imaging; CT= computed tomography
[b] = mean (range)
[c] n.m. = not mentioned

Figure 1. *Axial T_1-weighted MR images before (top) and one year after (bottom) radioiodine therapy. Note the tracheal compression by the intrathoracic part of the nodular goiter before and after radioiodine therapy (arrows). There is considerable improvement of tracheal compression one year after radioiodine therapy.*

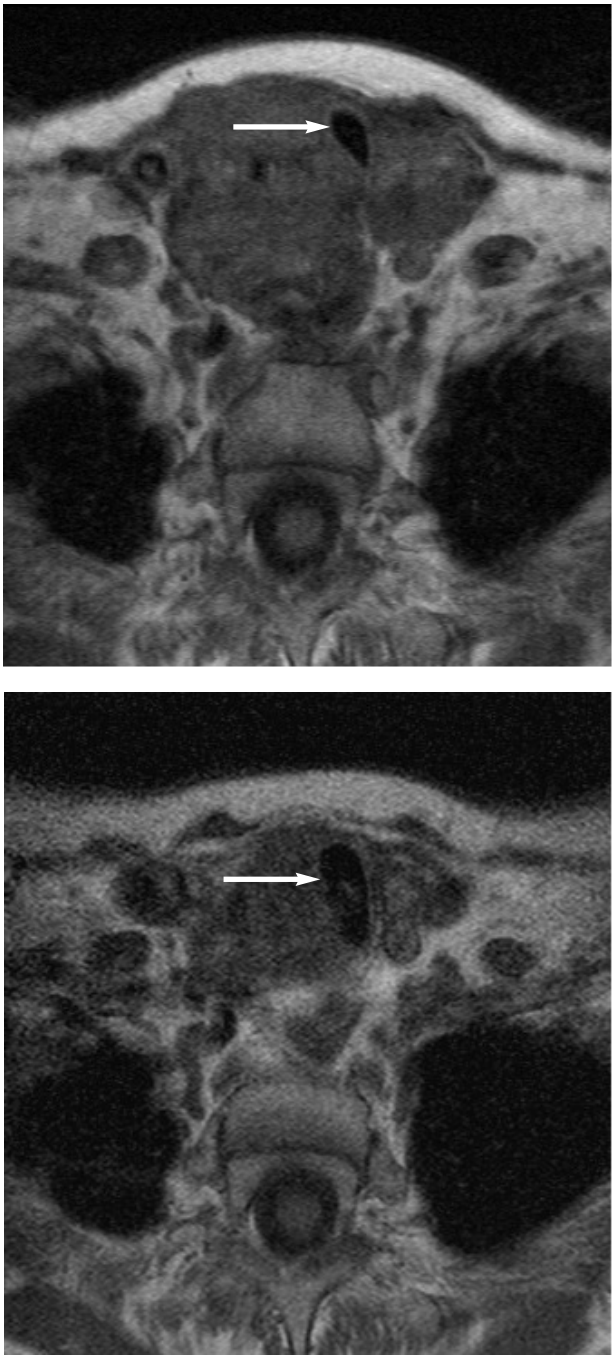
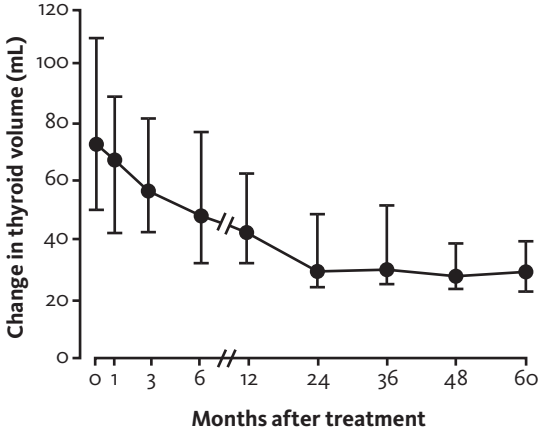


Figure 2. *Median thyroid volume before and after radioiodine treatment in 39 patients with nontoxic multinodular goiter who remained euthyroid after a single dose. Bars are quartiles. (From Nygaard B, Hegedüs L, Gervil M, et al.: Radioiodine treatment of multinodular non-toxic goitre. BMJ 1993; 307: 828).*



1.2

Thyrotropin (TSH)

1.2

Thyrotropin (TSH)

The function of the thyroid gland is regulated by TSH. This hormone is produced by the anterior pituitary gland. The pituitary cells that secrete TSH (thyrotrophs) are under control of neurons in the hypothalamus that secrete thyrotropin-releasing hormone (TRH). TRH is a tripeptide produced in cells in the nucleus paraventricularis of the hypothalamus. It is transported along their axons to nerve terminals in the median eminence of the hypothalamus. Here TRH is released into the hypophyseal portal blood and transported to the anterior pituitary gland. Other important regulators of TSH secretion are the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). They inhibit TSH secretion and to a lesser extent TRH secretion. TRH and the thyroid hormones maintain TSH secretion and therefore thyroid function remarkably constant. In this way the hypothalamic-pituitary-thyroid axis is a classic example of an endocrine feedback loop. Other regulators of TSH secretion, although less important, are somatostatin and dopamine, which inhibit TSH secretion, and α–adrenergic agonists which stimulate TSH secretion (34).

Thyroid stimulating activity has been extracted from the pituitaries of almost all mammalian species as well as from those of lower vertebrates. TSH preparations purified from pituitary glands contain heterogeneous components with variable biological activity. The molecular weights of these components are in the range of 28 to 30 kDa. The differences in molecular weight are caused by heterogeneity of carbohydrate chains of the TSH molecule (35).

TSH is a glycoprotein and consists of a heterodimer containing two noncovalently linked subunits: an α–subunit, which is common to the other glycoprotein hormones [luteinizing hormone (LH), follicle stimulating hormone (FSH) and human chorionic gonadotropin (HCG)] and a β–subunit, which is hormone-specific. The human α–subunit contains 92 amino acids and the human TSH β–subunit has an apoprotein core of 112 amino acids (36). Human TSH contains three aspargine linked oligosaccharide chains that, when fully processed, terminate either with sialic acid linked to galactose, or with sulfate attached to N-acetylgalactosamine. Two of these oligosaccharide chains are attached to the α–subunit and one is attached to the β–subunit. These oligosaccharide chains play an important role in biological activity and determine the metabolic clearance rate of TSH (37). The structures of the oligosaccharide chains of TSH are altered in different physiological and pathological states, resulting in alterations of the bioactivity of the hormone (38-41). For example, in hypothalamic hypothyroidism, secreted thyrotropin has impaired biologic activity because of impaired binding to its receptor. This suggests that TRH regulates not only the secretion of TSH, but also its specific molecular and conformational features required for hormone action (42-45). TRH

influences the carbohydrate structure of TSH. The glycosylated forms of TSH secreted after acute intravenous stimulation with TRH differ from the forms of TSH circulating in the steady state condition (46). Basal TSH has a different oligosaccharide composition from TSH in serum 30 min after TRH administration. Basal TSH has fewer core fucose residues and more exposed galactose residues than TSH released after acute TRH administration. The amounts of oligosaccharide branching and the amounts of N-acetylglucosamine were similar, whereas the degrees of sialylation for basal TSH and TRH-released TSH were highly variable. The biochemical differences detected in basal TSH vs. TRH-released TSH may reflect different post-translational processing and storage of these molecules in thyrotrophs. The release of particular isoforms of human TSH depending on TRH is an important principle in the physiological control of thyroid function by the pituitary.

Thyrotropin is released in a pulsatile manner and has a diurnal rhythm with the highest levels at night. It has a plasma half-life of approximately 30 min. TSH regulates not only the function of the thyroid follicular cells including thyroid hormone synthesis and secretion, but also the proliferation of thyroid cells. All actions of TSH follow binding of the molecule to its receptor (47-51). The TSH receptor, member of the G protein-coupled receptor family, is localized on the basal surface of the follicular cells of the thyroid. Binding of TSH to the receptor activates the adenylyl cyclase-cyclic AMP-protein kinase A pathway and the Ca-protein kinase C pathway (47-50).

1·3

Bovine and Human Cadaver Pituitary TSH

1·3

Bovine and Human Cadaver Pituitary TSH

Bovine and human cadaver pituitary TSH have been administered to humans. Despite the structural differences of TSH molecules between species, their thyrotropic activities are not species specific (35). Rationale for the use of bovine TSH (bTSH) in humans was obtained when similar binding and activity was seen for human and bovine TSH in the chick bioassay (52). Bovine TSH administration stimulates increases in the serum levels of T_4, T_3 and thyroglobulin (Tg) in humans (53,54). Also enhancement of thyroid radioiodine uptake in normal subjects following injection of either bovine or human pituitary TSH has been demonstrated (55,56). Pharmacokinetic studies showed a peak serum TSH concentration 4 hours after intramuscular (im) administration of bovine TSH. Ten hours after the administration of bovine TSH, serum TSH concentrations were half of the peak serum TSH levels. Initial results in thyroid cancer patients suggested that administration of bovine TSH was effective, although it did not stimulate radioiodine uptake as good as thyroid hormone withdrawal (57,58).

Local and systemic adverse events, such as local induration, urticaria, nausea and vomiting and anaphylactic shock, were associated with bovine TSH administration (40,59,60). These adverse effects were particularly evident in patients treated at multiple occasions. Because of these allergic reactions and the diminished effectiveness of the agent with repeated doses, patients were studied for the development of antibodies to bovine TSH (61-63). Indeed, anti-bovine TSH antibodies were detected in the sera of patients with thyroid carcinoma, after repeated administration of bovine TSH. Due to antibody formation development of resistance to bovine TSH appeared to be inevitable in patients who received repeated injections of this hormone (64). Antibodies of the IgG class, which bound both bovine TSH and human TSH, were detected using specific radioimmunoassays and radioimmunoelectrophoretic techniques in patients with thyroid carcinoma, who had received multiple injections of bovine TSH. Antibodies persisted for more than one year and binding of bovine TSH was greater than that of human TSH throughout this period. Characterization of these antibodies with respect to their binding to human and bovine glycoprotein hormones and subunits revealed two populations of antibodies, one which binds both bovine and human TSH, and one which binds only bovine TSH. Both antibodies appeared to be directed towards antigenic sites on the β–subunit of TSH, as both the human and the bovine TSH β–subunits displaced the binding of intact TSH from antibodies whereas the α–subunits were virtually unreactive. The binding studies suggested that the cross-reactivity of the antibody to human TSH occurred on the basis of common antigenic determinants on the β–subunits of the two species (65).

Neutralizing anti-bovine TSH antibodies developing in patients, who had received multiple doses of bovine TSH, also interfered with measurement of endogenous TSH levels. Less suppression of serum TSH levels was found in patients receiving adequate replacement therapy after thyroidectomy for thyroid carcinoma. This was due to interference of circulating anti-bovine TSH antibodies in the radioimmunoassay (66,67). This was truly hindering the ability to monitor the efficacy of thyroid hormone suppression therapy in thyroid cancer patients and may possibly result in the development of secondary hypothyroidism in patients with an intact thyroid gland. Because of the occurrence of allergic reactions and the relative ineffectiveness with multiple dosing due to the development of anti-TSH antibodies, bovine TSH has been abandoned for use in humans and is currently no longer available.

Preparations of purified human TSH extracted from human cadaver pituitary glands have been used as an alternative for bovine TSH (55). Preparations of human thyrotropin, prepared from human cadaver pituitary glands and highly purified using a monoclonal antibody technique, stimulate thyroid function (68), but disadvantages of human cadaver pituitary TSH are its limited availability and contamination of the preparation by other pituitary hormones and their subunits. Nowadays the administration of human pituitary cadaver TSH to patients is no longer advised because of the potential transmission of the agent for Creutzfeldt-Jacob disease and the risk of the development of this disease years later (69).

1·4

Recombinant Human Thyrotropin (rhTSH)

1·4

Recombinant Human Thyrotropin (rhTSH)

1.4.1 Development of and in vitro studies with rhTSH

The abovementioned problems with the use of bovine and human cadaver TSH have stimulated the development of rhTSH. TSH generated by recombinant DNA techniques would be far less likely to induce allergic reactions and TSH antibodies or cause transmission of infectious agents.

The human thyrotropin β–subunit gene was isolated and characterized from two genomic libraries (70,71). Chinese hamster ovary (CHO) cells co-transfected with two plasmids, one carrying the human α–subunit cDNA with mouse dihydrofolate reductase gene and the other carrying human TSH β–subunit cDNA have been used to produce rhTSH. Each cDNA was driven to expression under the control of a SV40 early promoter. rhTSH and its α–subunit were secreted into culture media, and their secretion increased with exposure of the cells to increasing concentrations of methotrexate (72). In an adenovirus transformed human embryonal kidney cell line, cotransfection of two virus vectors, each containing one subunit of human TSH, together with a plasmid containing the adenovirus VA RNA genes produced rhTSH as well as free human α– and TSH β–subunits (73).

Studies on the structure of rhTSH followed because gel filtration analysis revealed that the molecular size of the rhTSH was not the same as that of natural human TSH. The rhTSH synthesized was larger in molecular weight than standard human TSH preparation on gel chromatography suggesting an altered glycosylation pattern. The structure and particularly the glycosylation pattern of recombinant glycoproteins are influenced by the specific subclone and culture conditions used to produce the recombinant hormones. Since TSH and other recombinant proteins are expressed in non-human cell lines, they are likely to have different glycosylation patterns (72,73).

The investigators, who previously characterized rhTSH secreted by CHO cells after stable transfection of the human TSH β–gene, studied structure-function relationships of different isoforms of this glycoprotein (74). They produced rhTSH and quantitated it by immunoassays, receptor binding assays, and amino acid analysis and further characterized it by a variety of biochemical methods, including chromatofocusing and carbohydrate analysis. The results indicated that secreted rhTSH, similar to intrapituitary human TSH, was a mixture of isoforms, caused at least in part by the degree of sialylation. The degree of sialylation, highly dependent on the bioreactor production conditions, appears to be the major factor affecting bioactivity of rhTSH.

The contribution of the individual monosaccharides to hormonal activity was determined by sequential deglycosylation of rhTSH using exoglycosidases and by

studying the effect of resialylation of desialylated rhTSH using sialyltransferases (75). Sequential removal of sialic acid, galactose or N-acetylglucosamine resulted in a more than 10-fold increase in the in vitro bioactivity of rhTSH. The metabolic clearance of the derivatives was faster than that of intact hormone. Agalacto-rhTSH was cleared slower than asialo-rhTSH. However, the in vivo bioactivity decreased progressively with each monosaccharide removal. The increased in vitro cyclic AMP-stimulating activity, increased metabolic clearance and the decreased in vivo biologic activity were all reversed by resialylation of the terminal galactose residues. These results indicate that the bioactivities of rhTSH are modulated by terminal sialylation. The modification of the oligosaccharides by glycosidases and glycosyltransferases could be used as a powerful tool to delineate the function of carbohydrates in glycoproteins and to engineer more potent hormone analogues with a longer half-life and/or higher bioactivity.

Huber et al. (76) assessed the bioactivity of rhTSH using a human fetal thyroid cell culture. RhTSH caused a dose-related increase in human thyroid monolayer cell cAMP release and human thyroglobulin secretion, confirming its bioactivity. They derived an estimated biopotency for the rhTSH preparation examined of 5.6 U/mg compared to 10 U/mg for bovine TSH. The rhTSH had an immunologic activity similar to that of purified pituitary human TSH standards. Furthermore, rhTSH induced thyroid epithelial cell growth, as evidenced by a decrease in thyroid cell doubling time. Addition of rhTSH to cultures of rat FRTL-5 and bovine and fetal human thyroid epithelial cells stimulated adenylate cyclase activity. Thus, rhTSH appeared to be a potent glycoprotein hormone preparation when measured in a homologous human cell culture system (76). The demonstrated in vitro bioactivity of rhTSH as assessed by cAMP production, growth stimulation and 5'-deiodinase activity strongly suggested that rhTSH would be biologically active when administered in vivo.

The presence and specific structures of the oligosaccharide-side chains of TSH have been shown to be important for its bioactivity. Since the carbohydrate structure of a protein reflects the glycosylation apparatus of the host cells in which the protein is expressed the choice of the host cells is important. The biological activity of the purified recombinant human TSH preparation derived from a stable transfectant of CHO cells was studied most intensely (72,74,75,77).

The complementary DNAs for HCG-α and hTSH-β were cotransfected into CHO cells. Stable transfectants with a high rate of rhTSH production were selected and subsequently cultured on microcarrier beads. This genetically engineered cell line and the development of a reproducible process for the expression and purification of biologically active rhTSH were described by Cole et al. (78) from the Therapeutic Protein Development Department, Genzyme, Framingham MA, USA.

The TSH glycoprotein, which is produced by recombinant DNA technology, is at

this moment available as Thyrogen® (thyrotropin alfa for injection). It is supplied by Genzyme (Cambridge MA, USA) in vials, which contain each 1.1 mg thyrotropin alfa, and after reconstitution with 1.2 mL of sterile water, the thyrotropin alfa concentration is 0.9 mg/mL. The biological potency of rhTSH is expressed in units (U) that have been established in relation to the Second World Health Organization International Reference Preparation, Thyrotropin, Human, for Bioassay (84/70): 4.9 U/mg protein.

1.4.2 In vivo studies with rhTSH in animals

Thotakura et al. (77) used an in vivo rat model to examine the metabolic clearance of rhTSH. The recombinant TSH was derived from a stable transfectant of CHO cells and its carbohydrate composition showed to be more highly sialylated than cadaver-derived pituitary human TSH. No N-acetyl galactosamine was detectable in rhTSH, which implies the absence of terminal sulfate moieties, both of which are present in pituitary derived TSH. The investigators injected 0.5-1.0 µg of rhTSH and measured TSH concentrations at several time points. The rhTSH had a 2-fold lower metabolic clearance rate than pituitary TSH, resulting in a greater than 10-fold higher serum concentration of rhTSH at 3 hours as compared to pituitary human TSH. After sialic acid removal, the rhTSH was cleared faster (7.5-fold) than pituitary human TSH. Therefore the longer plasma half-life of rhTSH was due to its higher sialylation.

The same group used this in vivo rat model to investigate the role of terminal carbohydrate residues in organ distribution and metabolic clearance of TSH (79). They used different ^{125}I-labeled TSH preparations with distinct carbohydrate composition and injected them intravenous (iv) in the rats. At various time points after bolus TSH injection, blood, liver, kidney, spleen, lung, heart, and thyroid samples were collected. TSH uptake was determined by trichloroacetic acid precipitation of ^{125}I-TSH in the organ homogenates. The rhTSH was distributed predominantly to the kidneys. In contrast, purified human TSH and bovine TSH were cleared predominantly by the liver, with a later renal phase of clearance. The liver with only minor involvement of other organs cleared asialo-rhTSH. The early liver uptake was proportionally lowest for rhTSH, and correlated inversely with the serum levels and the degree of sialylation. Blockade of the N-acetylgalactosamine (GalNAc) sulfate receptors by injection of bovine LH resulted in a significant decrease in liver uptake of purified human TSH. Similarly, liver uptake of asialo-rhTSH was significantly inhibited by injection of asialo-fetuin. Thus, purified human TSH and bTSH preparations containing sulphated oligosaccharide chains are cleared at least in part by the GalNAc sulfate-specific receptors in the liver. In contrast, rhTSH with highly sialylated oligosaccharides in both subunits accumulates predominantly in the kidneys, even at the early phase of clearance, indicating that sialylated glycoprotein hormones escape from specific receptor-mediated

clearance mechanisms in the liver. These data indicate that terminal sialic acid and GalNAc sulfate residues, each to a different extent, determine glycoprotein hormone distribution and thereby its plasma level, which is a major factor in determining the in vivo potency of TSH.

A combined rat model of chronic catheterization and suppression of endogenous TSH release was used to study pulsatile effects of rhTSH (80). Pulsatile secretion of TSH is a well-characterized phenomenon in the human with only limited data from animal studies. Quantified pulses of different preparations of thyrotropin were applied iv with minimal interference with endogenously produced hormone. The rats pretreated with drinking water containing T_3 showed a significant 6-fold decrease of rat TSH after four days and their free thyroxine (FT_4) levels were 9-fold below unsuppressed levels. FT_4 response to exogenous TSH application above this suppressed baseline level was selected as an endpoint. Infusion studies compared pulsatile with continuous TSH administration. A low and a high dose of rat TSH and rhTSH were administered. Levels of FT_4 were compared after two and four days and responsiveness to a standard high bolus of rat TSH 6 h after end of infusion was assessed. With regard to its potency for FT_4 release, a general trend to superior efficacy of pulsatile TSH stimulation of the thyroid gland in comparison to continuous stimulation could be observed in all four experiments. More pronounced effects were seen after 2 and 4 days of infusion with high doses of rat TSH and after 4 days of infusion with low doses of rhTSH. Comparison of FT_4 responses to rhTSH boli showed a 2- and 6-fold higher response in the pulsatile group compared to the continuous group after low and high rhTSH infusion, respectively.

The thyroid stimulatory effect of rhTSH has also been studied in mice (81). Like in the rat in vivo model the mice were given T_3 in their drinking water to suppress endogenous TSH. Various doses of exogenous pituitary and rhTSH preparations were injected intraperitoneally and blood samples were obtained from the orbital sinus 6 h later. The T_4 level served as the end-point and the maximal level of T_4 after TSH stimulation was similar to that observed in normal, nonsuppressed mice. The assay required injection of approximately 3.0 µg of pituitary human TSH, 1.0 µg rhTSH, 0.2 µg bovine TSH, and 0.1 µg rat TSH to attain half-maximal responses.

Colzani et al. (82) determined the biological activity of rhTSH in euthyroid and in T_3-treated, TSH-suppressed rats and mice. Doses of rhTSH based on body weight were used (≈0.03 mg/rat and ≈0.003 mg/mouse). The rhTSH was administered intraperitoneally and resulted in similar serum rhTSH concentrations in the rats and mice. Euthyroid and TSH-suppressed mice responded to rhTSH administration with increases in serum T_4 , but serum T_4 did not increase after rhTSH administration in euthyroid rats. In TSH-suppressed rats, the increase in serum T_4 was

similar to that observed in TSH suppressed mice. These observations suggest that rhTSH more readily displaces endogenous TSH from the mouse than from the rat thyroid TSH receptor, because equal responses were observed when endogenous TSH was suppressed. Three hours after administration of rhTSH, ^{125}I was administered to the rodents and the uptake of radioiodine in the thyroid was measured 2 h later. These uptakes were compared to the 2-h uptakes in rats and mice without rhTSH pretreatment. Euthyroid rats with and without rhTSH pretreatment did not show differences in thyroid radioiodine uptake. In contrast, in euthyroid mice that had received rhTSH, the 2-h ^{125}I uptake was significantly decreased. RhTSH administration did not affect the very low 2-h thyroid ^{125}I uptake in TSH-suppressed rats, but did result in a small but significant increase in TSH-suppressed mice.

Finally, in vivo animal studies were carried out in rhesus monkeys and investigated the half-life of rhTSH and its ability to stimulate thyroid function in these animals (83). The clearance of rhTSH after iv administration of 2 U rhTSH (≈0.4 mg) in two monkeys showed a rapid first phase with a half-life of approximately 63 minutes, followed by a slow second phase with a half-life of 326 minutes. Serum T_4 and T_3 concentrations increased at 3 h and remained elevated 24 h after rhTSH administration. Intramuscular administration of the same dose of rhTSH resulted in a marked elevation of serum TSH and increases in serum T_4 and serum T_3 levels 2-3 times above baseline. 6-h and 20-h thyroid ^{123}I uptake was measured at baseline and 5 h after rhTSH administration. Both uptake values were increased in one monkey but did not change in the other monkey. Two other monkeys received three daily im injections of 2 U rhTSH. In these monkeys serum T_4 concentrations increased several-fold and serum T_3 increased 2-3 times above basal values. The 6-h and 20-h thyroid ^{123}I uptake was measured at baseline and 19 h after rhTSH administration. Both values approximately doubled in both monkeys. These results demonstrated the biological efficacy of rhTSH administered to rhesus monkeys and strongly suggested that rhTSH would be effective in stimulating thyroid function in man. However, the biological potency of rhTSH in humans was expected to be much stronger, since they would be more sensitive to rhTSH than animals.

Since the publication of this last study, articles were published discussing the use of rhTSH in animals for veterinary purposes. The effects of rhTSH on serum T_4 in euthyroid beagle dogs were described (84). TSH response tests were performed by using total doses of 0.025 mg, 0.05 mg, and 0.1 mg rhTSH, administered iv. Thereafter, TSH response tests were performed by using 0.05 mg of rhTSH administered by im and subcutanous (sc) routes, respectively. Following all the administered doses of rhTSH, an increase in the serum T_4 concentration was noted, although this increase was not always statistically significant. Based on this study, 0.05 mg was judged to be the optimal intravenous dose of rhTSH.

Recently, the response of euthyroid cats to the administration of rhTSH was published (85). Seven healthy cats received each of 5 doses of rhTSH (0, 0.025, 0.050, 0.100, and 0.200 mg), iv, at 1-week intervals. Serum concentrations of T_4 and FT_4 were measured immediately before each injection and 2, 4, 6, and 8 hours after administration of each dose. Overall T_4 response did not differ significantly among cats when administered doses were higher than or equal to 0.025 mg. Serum T_4 concentrations peaked 6 to 8 hours after administration for all doses higher than or equal to 0.025 mg. For all doses higher than or equal to 0.025 mg, mean ± SEM T_4 concentrations at 0, 6, and 8 hours were 33.9 ± 1.7, 101.8 ± 5.9, and 101.5 ± 5.7 nmol/L, respectively. For all doses higher than or equal to 0.025 mg, mean FT_4 concentrations at 0, 6, and 8 hours were 38.7 ± 2.9, 104.5 ± 7.6, and 100.4 ± 8.0 pmol/L, respectively. At 8 hours, the FT_4 response to 0.025 and 0.050 mg was less than the response to 0.100 and 0.200 mg. It is concluded that the TSH stimulation test can be performed in cats by iv administration of 0.025 to 0.200 mg of rhTSH and measurement of serum T_4 concentrations at time of injection and 6 or 8 hours later.

1.4.3 In vivo studies with rhTSH in humans

Six normal volunteers, two men and four women, without evidence of thyroid disease, including normal serum free T_4 indexes and TSH concentrations and negative tests for antibodies to thyroid peroxidase and Tg were studied by Ramirez et al. (86). They were the first to report on the effects of rhTSH on serum thyroid hormone and Tg concentrations in normal subjects. Each individual received 0.1 mg rhTSH im. Blood was obtained before, 2, 4, and 8 h after, and 1, 2, 3, 4, 7, and about 21 days after rhTSH administration. Serum TSH was significantly increased at 2 h (40.7 ± 7.4 mU/L, mean ± SE), peaked at 4 h (50.9 ± 9.3 mU/L), remained significantly elevated for 1 day, and was significantly below baseline (0.8 ± 0.5 mU/L) 7 days after rhTSH administration. Serum T_3 was significantly increased at 4 h (basal value 115 ± 4 ng/dL; 4 h value 190 ± 14 ng/dL), peaked at 24 h (217 ± 23 ng/dL), and remained significantly elevated for 3 days. Serum T_4 was significantly increased at 8 h (basal value 7.3 ± 0.2 mg/dL; 8h value 9.8 ± 0.4 mg/dL), peaked at 24 h (11.2 ± 0.5 mg/dL), and remained significantly elevated for 4 days. Serum Tg did not change for the first 8 h, increased significantly at 1 day (basal value 15.9± 3.9 ng/mL; 1 day value 34.7 ± 6.0 ng/mL), peaked at 2 days (44.2 ± 7.0 ng/mL), and remained significantly elevated for 4 days. All values returned to baseline at 3 weeks. TSH antibodies were not detected at 3 weeks. Except for mild soreness at the injection site, all subjects tolerated the rhTSH well. The study demonstrated that a single dose of 0.1 mg rhTSH was a potent stimulator of thyroid function in normal healthy subjects.

Torres et al. (87) determined the effects of doses higher than 0.1 mg of rhTSH on thyroid hormone and Tg secretion. Six normal subjects with no evidence of thy-

roid disease received either 0.3 or 0.9 mg rhTSH by im injection. Serum TSH, T_4, T_3, and Tg concentrations were measured at 2, 4, and 8 h and at 1, 2, 3, 4, and 7 days after rhTSH administration. The peak serum TSH concentrations were 82 ± 18 and 277 ± 89 mU/L, respectively, for the 0.3 mg and 0.9 mg doses of rhTSH. Serum T_4, T_3, and Tg concentrations increased significantly in subjects receiving 0.3 and 0.9 mg rhTSH, with significant increases in T_4 and T_3 being observed before significant increases in serum Tg. Peak concentrations of serum T_4, T_3, and Tg, after 0.3 mg rhTSH administration, were 100 ± 19, 131 ± 14, and 1035 ± 724% above individual baseline values, respectively. Similarly, peak concentrations of serum T_4, T_3, and Tg, after 0.9 mg rhTSH administration, were 102 ± 16, 134 ± 7, and 1890 ± 768% above individual baseline values. These data, compared with the previously reported data for the responses to 0.1 mg rhTSH, indicated that 0.1, 0.3, and 0.9 mg rhTSH had the same stimulatory effects on thyroid hormone and Tg secretion, except that the T_4 response was greater in groups receiving 0.3 or 0.9 mg rhTSH than in the group receiving 0.1 mg rhTSH. According to these studies a single dose of rhTSH greater than 0.1 mg did not seem to further enhance thyroid hormone secretion in normal volunteers. This group of investigators also studied the effect of rhTSH on thyroid radioactive iodine uptake (RAIU) in the group that received 0.9 mg rhTSH. The 6-h and 24-h RAIU values were significantly higher after rhTSH (the pre-rhTSH, 6 h value was 12.5 ± 1.8% and the 24 h value was 23 ± 2.7%; the post-rhTSH, 6 h value was 27 ± 4.8% and the 24 h value was 41 ± 4.2%). The stimulatory effects of 0.9 mg rhTSH on the 6 h and 24 h RAIUs were similar.

The next question addressed in normal subjects was whether rhTSH administration prior to ^{123}I would increase the low thyroid RAIU in subjects treated with sodium iodide (88). Nine euthyroid men were given 15 mg iodide daily for 7 days. There was a marked increase in serum TSH values 8 and 24 hours after rhTSH administration, which induced elevated serum T_4 and T_3 concentrations. A 16 hour thyroid RAIU was measured at baseline, after 5 days of iodide administration, and either 8 or 32 hours after im administration of rhTSH. Administration of rhTSH 8 hours before ^{123}I to 4 subjects increased the 16 hour thyroid RAIU by 62% above the low post iodide thyroid RAIU. Administration of rhTSH 32 hours before ^{123}I administration to 5 subjects increased the 16 hour thyroid RAIU by 97% above the low post-iodide thyroid RAIU. The mean increase in the 16-h thyroid RAIU was 88% in the 9 subjects. As rhTSH increased the thyroid RAIU in subjects with depressed thyroid RAIUs during iodide administration, rhTSH pretreatment may be useful in preparing patients with low thyroid RAIUs due to excess iodine before radioactive iodine treatment.

Recently the effect of 0.9 mg rhTSH on thyroid size was studied in 9 male healthy euthyroid individuals (89). Thyroid volume was measured by ultrasonography at baseline and 4 h and 1, 2, 4, 7 and 28 days after the administration of 0.9 mg rhTSH. Twenty-four hours after rhTSH administration thyroid volume was

increased by 23.5 ± 5.5% and after 48 hours by 35.5 ± 18.4%. At day 4 the thyroid was again of normal size, and at day 28 the gland was reduced by 14.7 ± 3.8% compared with baseline thyroid volume.

1.4.4 rhTSH as an adjunct to radioiodine whole body scintigraphy and thyroglobulin testing after thyroidectomy for differentiated thyroid cancer

1.4.4.1 Introduction

Five to 15% of patients treated for differentiated thyroid carcinoma will develop a local recurrence and/or neck metastases and 10 to 15% will have distant metastases during follow-up (90). Diagnostic studies used for follow-up of thyroid cancer patients are radioiodine whole body scintigraphy (WBS) and serum Tg measurements. In patients who have been treated for differentiated thyroid carcinoma by (near-)total thyroidectomy radioiodine WBS can show the presence of residual normal thyroid tissue or thyroid carcinoma tissue in the neck or elsewhere in the body. It can also help to determine whether treatment with ^{131}I is useful. Dosimetric calculations can be made using scintigraphic measurements and radioactivity measurements in blood and urine samples in order to determine the therapeutic amount of radioiodine to be administered (91,92). The introduction of serum Tg measurements has allowed for a decrease in the frequency of radioiodine WBS, especially in patients at low risk for recurrence of the disease (2,90,93-95).

Some patient preparations are important to optimize the sensitivity of radioiodine whole body scintigraphy. A high serum TSH level (more than 25-30 mU/L) is needed to optimally stimulate radioiodine uptake in residual normal thyroid tissue and in thyroid carcinoma tissue (96). After (near-)total thyroidectomy this is usually reached within 4 to 6 weeks (97). In patients who use thyroid hormone, levothyroxine (L-T_4) should be stopped for about 4 weeks and levotriiodothyronine (L-T_3), because of its shorter half-life, for 10 to 14 days (97,98). Serum TSH levels should always be verified as being at least 25-30 mU/l before imaging is carried out. The sensitivity of serum Tg measurements for the detection of residual/recurrent thyroid cancer is also higher when the serum TSH level is high.

Diagnostic radioiodine whole body scintigraphy and Tg testing for detection of residual or remnant thyroid carcinoma in thyroidectomized patients is traditionally done after withdrawal of thyroid hormone therapy, subjecting the patients to hypothyroidism for several weeks (2,90,95). This hypothyroid state often results in discomfort and morbidity and therefore has a major negative impact on the quality of life. This is an important issue, as patients with thyroid cancer usually have a good prognosis. Dow et al. (99) evaluated the impact of thyroid hormone withdrawal on patients' perceived changes in quality of life in 34 subjects (mean age

40 years) undergoing thyroid hormone withdrawal in preparation for scanning procedures. They used a new instrument, the Quality of Life (QOL)-Thyroid scale, and an established instrument, the Functional Assessment in Cancer Therapy-General, at four specific time points in relationship to scanning. Thyroid hormone withdrawal caused significant changes in physical, psychological, and social well-being across the four testing points. Whereas the physical symptoms related to thyroid hormone withdrawal are generally acknowledged, this study showed that patients also suffer from negative psychological, family, and work sequelae.

Moreover, in some patients, especially those with intracranial or intraspinal metastases, serious complications can occur due to accelerated tumor growth during thyroid hormone withdrawal. An elegant solution to the problems of thyroid hormone withdrawal is whole body scintigraphy and Tg testing after the administration of rhTSH, which makes it possible to conduct radioiodine whole body scintigraphy and sensitive serum Tg testing without discontinuing thyroid hormone therapy.

1.4.4.2 rhTSH-stimulated radioiodine whole body scintigraphy combined with thyroglobulin testing after thyroidectomy for differentiated thyroid cancer

In a phase I/II study (100), the preliminary efficacy of rhTSH was assessed in 19 patients with differentiated thyroid cancer. In these patients 7 different dosing regimens of rhTSH were used: im administration of 10 U/day (≈2.0 mg; 1, 2 or 3 days), 20 U/day (1 or 2 days), 30 U/day (1 day) or 40 U/day (1 day). Twenty-four h after the last dose of rhTSH, 1-2 mCi ^{131}I was administered, 48 h later followed by WBS. After discontinuing L-T_3 for a median period of 19 days, the endogenous serum TSH levels were above 25 mU/L. Then a second dose of ^{131}I was given to the patients and they were rescanned 48 h later. Mean peak levels of serum TSH after a single dose of 10, 20, or 30 U of rhTSH were 127, 309 and 510 mU/L, respectively, and occurred 2-8 h after injection. A single injection of 40 U in 1 patient led to a peak TSH level of 505 mU/L. Twenty-four h after the injection mean TSH levels decreased to 83, 173 and 463 mU/L in the respective treatment groups. The rhTSH was tolerated well, but in the patients receiving the highest doses (30 or 40 U) nausea and vomiting was reported (21%). In 63% of the patients, the scans after rhTSH treatment and in the hypothyroid state showed complete concordance. In 3 patients additional sites of uptake, two in the chest and one in the thyroid bed, not visible on the scans during hypothyroidism, were identified after rhTSH. In 1 patient, a focus of uptake was better visualized after rhTSH than after withdrawal. In 3 other patients, 1 lesion in the chest and 2 in the neck, were seen only after withdrawal. Serum Tg levels more than doubled in response to rhTSH in 58% of the patients and in 79% after withdrawal. The increase was lower after rhTSH in 93% of the patients. These data showed that rhTSH could be safely and effectively given to patients after thyroidectomy for thyroid cancer to stimulate ^{131}I uptake

and Tg secretion. It was concluded that further investigations using different time intervals between rhTSH injections and ^{131}I administration or Tg measurement were needed to define optimal conditions for these diagnostic tests.

The use of rhTSH has been investigated in two phase III studies. In the first phase III trial (101), 127 patients with thyroid cancer underwent radioiodine WBS (using 2 to 4 mCi ^{131}I) by two techniques: first after receiving two doses of 0.9 mg of rhTSH administered with an interval of 24 hours while thyroid hormone therapy was continued and second after the withdrawal of thyroid hormone therapy, while no rhTSH was administered. In 62 of the 127 patients radioiodine WBS by one or both techniques were positive. The scintigrams obtained after administration of rhTSH were equivalent to the scintigrams obtained after withdrawal of thyroid hormone in 41 of these 62 patients (66%), superior in 3 (5%), and inferior in 18 (29%). When the 65 patients with negative WBS by both techniques were included, the two scintigrams were equivalent in 106 patients (83%). Eight patients (13% of those with at least one positive scintigram) were treated with radioiodine on the basis of superior scintigrams obtained after withdrawal of thyroid hormone therapy. As expected, patients had more symptoms of hypothyroidism and dysphoric mood states after withdrawal of thyroid hormone than after administration of rhTSH.

In the second phase III study (102), a total of 229 patients with differentiated thyroid carcinoma were treated with rhTSH and randomized in either one of two dosing regimes: 0.9 mg rhTSH, im, every 24 h for two doses or every 72 h for three doses. This study also formally examined the utility of rhTSH in TSH-stimulated Tg testing and the value of the combination of radioiodine WBS and Tg testing after administration of rhTSH for detecting thyroid carcinoma. For this second phase III study a higher scanning dose of ^{131}I (4 mCi) was chosen, based on results of an evaluation conducted in a subset of patients of the first phase III study that indicated that the clearance rate of radioiodine was greater in the euthyroid state than when patients were hypothyroid. Stricter scintigraphy protocols were used for acquiring WBS and a more clinically relevant definition of equivalent scans was used. Furthermore, in this trial more patients with metastatic disease were enrolled. Radioiodine WBS and serum Tg measurements were performed after administration of rhTSH and again after thyroid hormone withdrawal in each patient. Like in the earlier trials, 24 h after the last rhTSH injection radioiodine was administered and 48 h later WBS was obtained. Two weeks after the last rhTSH dose, patients were withdrawn from thyroid hormone therapy until adequate hypothyroidism (TSH > 25 mU/L) was achieved. Serum Tg was measured on the final day of rhTSH administration and 24, 48, 72 h and 7 days after the final dose and during the withdrawal phase on the day of radioiodine administration. Radioiodine WBS was concordant between the rhTSH-stimulated and thyroid hormone withdrawal phases in 195 of 220 patients with evaluable scans (89%). Of the

discordant scans, 8 (3%) had superior scans after rhTSH administration ands 17 (8%) had superior scans after thyroid hormone withdrawal. There was no difference in the number of superior rhTSH or withdrawal scans within either study arm or between the arms. Based on a serum Tg level of 2 ng/mL or more, thyroid tissue or cancer was detected during thyroid hormone therapy in 22%, after rhTSH stimulation in 52%, and after thyroid hormone withdrawal in 56% of patients with disease or thyroid tissue limited to the thyroid bed and in 80%, 100% and 100% of patients, respectively, with metastatic disease. The combination of radioiodine WBS and serum Tg after rhTSH stimulation detected thyroid tissue or cancer in 93% of patients with disease or thyroid tissue limited to the thyroid bed and in 100% of patients with metastatic disease (i.e., disease outside the thyroid bed). In both dosing regimens the combination of radioiodine WBS and Tg testing after administration of rhTSH did not miss any patient with metastatic disease. The patients reported a better quality of life after rhTSH administration compared with that after thyroid hormone withdrawal. No serious adverse events were related to rhTSH and none of the patients developed antibodies to rhTSH.

A caveat regarding the conclusions of the two phase III trials is the fact that few patients with distant metastases were included, raising questions about the applicability to high-risk patients. Robbins et al. (103) performed a retrospective analysis of a cohort of 289 patients undergoing routine follow-up testing to detect recurrent differentiated thyroid carcinoma over a 2-year period in which one group was prepared for testing by thyroid hormone withdrawal (161 patients), and the other group (128 patients) received rhTSH before the diagnostic tests. The cohort consisted of a relatively high number of high-risk patients in both arms (T4 tumors in 42% and 41% respectively, distant metastases in 18% and 23% respectively). The patients were examined by both radioiodine WBS and measurement of serum Tg. Patients with only thyroid bed uptake were excluded. The authors were unable to demonstrate a difference in the diagnostic accuracy of diagnostic whole body scanning and Tg testing between patients prepared by either thyroid hormone withdrawal or rhTSH. There were however two biases in this trial. First, patients were only offered rhTSH if they qualified for a compassionate need trial. Second, patients who had previously experienced the hypothyroid state may have been more likely to choose rhTSH.

1.4.4.3 rhTSH-stimulated thyroglobulin testing without radioiodine whole body scintigraphy after thyroidectomy for differentiated thyroid cancer

The sensitivity of a diagnostic ^{131}I whole body scan during follow-up after initial thyroid ablation is limited (104,105). Therefore, the utility of rhTSH-stimulated serum Tg measurements without radioiodine WBS in patients with undetectable serum Tg values on thyroid hormone therapy, as a method to differentiate

patients with persistent or recurrent disease from patients who are disease-free, has been studied (106-111).

David et al. (106) reported the results of rhTSH administration in 33 patients who underwent WBS and serum Tg measurement after rhTSH administration. These patients were divided into 2 groups depending on serum Tg concentrations during thyroid hormone therapy: 29 patients had Tg concentrations of <2 ng/mL and 4 patients had Tg values of >2 ng/mL. In the first group, Tg values remained <2 ng/mL in 25 patients and increased to 22.0 ± 5.75 ng/mL in 4 patients after rhTSH administration. WBS did not reveal any uptake of ^{131}I in the 25 patients without an increase in Tg, whereas ^{131}I uptake was evident in 2 of the 4 patients with a rise in Tg. In the second group Tg values increased in all 4 patients from 17.3 ± 6.35 ng/mL to 55.3 ± 12.75 ng/mL, and ^{131}I uptake was evident in 3 of the 4 patients. In this study it was concluded that rhTSH should be administered in TSH-suppressed patients with basal serum Tg concentrations of <2 ng/mL, because the increment in serum Tg concentrations can reveal the persistence of thyroid tissue in these patients.

In a prospective study by Pacini et al. (107) serum Tg measurement after rhTSH was compared with diagnostic radioiodine WBS and serum Tg measurement after thyroid hormone withdrawal in 72 patients who had a serum Tg < 1 ng/mL on thyroid hormone. A negative rhTSH Tg test was concordant with an undetectable Tg after thyroid hormone withdrawal in 88% (36 of 41 patients). In 12% (5 of 41 patients) Tg was detectable (1.1–7.8 ng/mL) only after thyroid hormone withdrawal and not after rhTSH stimulation. This was associated with negative radioiodine WBS (n=3) or a faint uptake in the thyroid bed (n=2). In 31 patients, Tg was detectable both after rhTSH and after withdrawal. The authors concluded that in patients with undetectable baseline levels of serum Tg and without anti-Tg antibodies, rhTSH-stimulated Tg represents an informative test to distinguish disease-free patients from patients with local disease or distant metastases.

Haugen et al. (108) reviewed their experience using rhTSH in 83 patients to compare the clinical relevance of a positive WBS and/or Tg. Ten patients had a positive WBS; eight of these patients had activity limited to the thyroid bed. rhTSH-stimulated Tg was 2 ng/mL or more in 25 and 5 ng/mL or more in 13 patients. Of the patients with a negative WBS, 11 of 20 patients with a Tg 2 ng/mL or more and 7 of 9 patients with a Tg 5 ng/mL or more received therapy or further evaluation based on the Tg results alone. Conversely, only 1 of 5 patients with a serum Tg less than 2 ng/mL received therapy or further evaluation based on a positive WBS alone. Three of the patients who did not receive therapy or further evaluation, had subsequent negative WBS 10-12 months later, suggesting lack of clinically significant disease. Twenty patients had a negative WBS and serum Tg 2 ng/mL or more.

Eleven of 20 patients had a Tg less than 5 ng/mL and 4 of these patients had further evaluation with a neck ultrasound. One patient had a biopsy-proven recurrence (rhTSH-stimulated Tg 4 ng/mL). Subsequent evaluations (at least 6 months later) have been negative for 8 patients. Of the nine patients with a Tg 5 ng/mL or more and a negative WBS, 7 had further evaluation and in 6 of 7 disease was identified. rhTSH-stimulated WBS and Tg showed to be complementary, but Tg is a more sensitive indicator of disease recurrence or persistence.

Mazzaferri and Kloos (109) retrospectively studied 107 consecutive patients with undetectable Tg levels on thyroid hormone therapy and without anti-Tg antibodies, who underwent rhTSH-stimulated testing 10 months to 35 years after thyroidectomy and ablation. 50% of the patients were at high risk of tumor recurrence and 5 had developed distant metastases during the course of their disease. Nine patients were found to have local disease or distant metastases identified by cytology, surgical pathology, post-therapy WBS, or CT. All of these patients had rhTSH-stimulated serum Tg levels above 2 ng/mL. In 11 other patients with rhTSH-stimulated Tg levels above 2 ng/mL, tumor could not be found. Thus tumor amenable to early therapy may be found when rhTSH-stimulated serum Tg rises above 2 ng/mL without performing a WBS.

Retrospectively Robbins et al. (110) analyzed the data of 366 patients who were evaluated with diagnostic WBS and serum Tg after preparation by rhTSH. In the entire group, 14% of 175 patients with a stimulated Tg level ≤ 2 ng/mL, and 76% of 191 patients with a stimulated Tg level > 2 ng/mL were found to have persistent/recurrent disease. A low risk group was defined (low probability of thyroid remnant, no previously diagnosed metastases, serum Tg on thyroid hormone < 2 ng/mL, no anti-Tg antibodies, AJCC stage I or II, post ^{131}I ablation). In this low risk group the negative predictive value of a stimulated Tg level ≤ 2 ng/mL was 91.7% (75/90 = 83% of these patients was found to have persistent disease). The authors concluded that a rhTSH-stimulated Tg of ≤ 2 ng/mL excluded persistent or recurrent disease in low risk patients, especially in those who had a prior negative diagnostic WBS.

In a meta-analysis of the studies mentioned above (112), it has been shown that tumor is rarely found when the serum Tg level is less than 2 ng/mL after thyroid hormone withdrawal (104,105) or after rhTSH stimulation (100-103,107,109,110,113). Patients with residual tumor are almost always identified by a serum Tg level above 2 ng/mL after thyroid hormone withdrawal (104,105) or rhTSH stimulation (100-103,107,109,110,113). The sensitivity of a rhTSH-stimulated serum Tg >2 ng/mL for the detection of thyroid cancer metastases was 91% (100-103,107,109,110,113), whereas the sensitivity of diagnostic whole body scanning, either after rhTSH or thyroid hormone withdrawal, was only 19%. In 168 of 784 patients whose serum Tg

on thyroid hormone suppression therapy was less than 1 ng/mL, serum Tg rose to >2 ng/mL after rhTSH stimulation. In 36% of these 168 patients, unsuspected metastases were found (36% at distant sites).

1.4.4.4 rhTSH-stimulated thyroglobulin testing with neck ultrasonography after thyroidectomy for differentiated thyroid cancer

The rhTSH-stimulated Tg test combined with neck ultrasonography appears to have the highest diagnostic accuracy in detecting persistent disease in the follow-up of patients with differentiated thyroid carcinoma (113,114). In the study by Pacini et al. (113), the addition of neck US increased the sensitivity for the detection of thyroid cancer metastases of rhTSH-stimulated serum Tg measurements from 85% to 96%. Torlontano et al. (114) also found that neck US showed metastases in lymph nodes in some patients with low rhTSH-stimulated serum Tg levels: in 2 of 5 patients with rhTSH-stimulated serum Tg levels 1–5 ng/mL and in 2 of 78 patients with undetectable rhTSH-stimulated serum Tg levels. Therefore, a detectable level of serum Tg on thyroid hormone therapy, its conversion from undetectable to detectable after rhTSH, and/or a suspicious finding at neck US allowed the identification of patients requiring therapeutic procedures without the need for a diagnostic WBS.

Follow-up protocols for patients with differentiated thyroid cancer are mainly based on data from high-risk patients treated in the past. However, the spectrum of patients with differentiated thyroid cancer has changed over the years, due to the fact that a larger number of thyroid tumors, mainly papillary, are being discovered at an earlier stage. Nowadays, the majority of patients are at low risk of recurrence. A consensus report of mainly American thyroid cancer specialists was published in 2003 (112), and a review article by European thyroid cancer specialists was published in 2004 (115), both containing new protocols for the follow-up of patients with differentiated thyroid cancer who are at low risk of recurrence. The new recommendations in these publications are based on three sets of data, which have been discussed above: data on the high sensitivity of serum Tg measurements after TSH-stimulation (after thyroid hormone withdrawal or after rhTSH), data on the limited sensitivity of diagnostic WBS, and data on the high sensitivity of ultrasound for the detection of lymph node metastases of thyroid cancer in the neck. In both the American and the European recommendations, it is advised in low-risk patients who are clinically disease-free 0.5 to 1 year after thyroidectomy and radioiodine ablation and whose serum Tg level on thyroid hormone suppression therapy is undetectable, to measure a rhTSH-stimulated serum Tg level, without WBS. Further follow-up and/or therapy are dependent on the rhTSH-stimulated Tg level, in combination with the results of US of the neck.

1.4.5 rhTSH as an adjunct to positron emission tomography for differentiated thyroid cancer

In differentiated thyroid cancer patients known to have disease based on an elevated serum Tg level, but with a negative WBS, localization of the disease is difficult. Progressive dedifferentiation of thyroid cancer cells leads to the loss of iodine-concentrating ability, wich results in a false negative WBS. Wang et al. (116) performed [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (FDG-PET) in 37 patients with differentiated thyroid cancer after surgery and ^{131}I ablation, who had a negative diagnostic WBS during routine follow-up. Serum Tg, Tg autoantibodies, neck ultrasound, and other clinically indicated imaging procedures were performed to detect residual disease. In patients with elevated Tg levels, FDG-PET localized occult disease in 71%, was false positive in one, and false negative in five patients. The majority of false negative FDG-PET scans occurred in patients with minimal cervical adenopathy. Thus, FDG-PET was able to localize residual thyroid cancer lesions in patients who had negative diagnostic ^{131}I WBS and elevated Tg levels, although it was not sensitive enough to detect minimal residual disease in cervical nodes. Results of FDG-PET during TSH suppression and during endogenous TSH stimulation were compared in two studies (117,118). Most locally recurrent and metastatic differentiated thyroid carcinomas exhibited a significant increase in FDG uptake on TSH stimulation. In 3 of 10 patients (117) and 3 of 8 patients (118), respectively, TSH stimulation resulted in detection of new lesions. Therefore it was recommended that FDG-PET examinations to detect metastatic or locally recurrent differentiated thyroid carcinoma should be performed during TSH stimulation.

These results are in line with the observation that TSH stimulates thyroidal glucose transporter expression. As a next step the idea of using rhTSH to improve the results of FDG-PET scanning has been explored. Petrich et al. (119) studied whether the administration of rhTSH stimulates FDG uptake in thyroid carcinoma lesions. Thirty patients with positive Tg levels and negative ^{131}I WBS underwent FDG-PET during TSH suppression and during rhTSH stimulation. FDG uptake was quantitated using tumor to background ratios (TBRs) and standardized uptake values (SUVs). During TSH suppression, there was focal FDG accumulation in 9 subjects and the total number of foci was 45. After rhTSH stimulation, the number of patients in whom FDG foci were detected was 19, and the number of foci identified was 82. TBRs and SUVs of regions showing positive FDG contrast were significantly higher during rhTSH stimulation than during TSH suppression. Recently, a prospective study on the effect of rhTSH as an adjuvant to FDG-PET in patients with residual or recurrent thyroid cancer was published (120). Seven patients with differentiated thyroid carcinoma, negative ^{131}I WBS, and biochemical evidence of residual disease were randomized and prospectively studied with FDG-PET both during thyroid hormone suppression and rhTSH stimulation. All

lesions seen on the TSH suppression scans were seen on the rhTSH stimulation studies. RhTSH stimulation identified four additional lesions not seen during TSH suppression. One patient was positive during rhTSH stimulation alone. The TBRs were significantly higher during rhTSH stimulation, compared with those during TSH suppression. These studies provided evidence that FDG-PET is more accurate during rhTSH stimulation than during TSH suppression to detect differentiated thyroid carcinoma.

1.4.6 rhTSH as an adjunct to radioiodine ablation of thyroid remnants in differentiated thyroid cancer

Radioiodine ablation of thyroid remnants after thyroidectomy for differentiated thyroid carcinoma improves the sensitivity of subsequent serum Tg measurements and radioiodine WBS for detection of residual thyroid carcinoma. The use of ^{131}I for radioablative treatment of thyroid remnants in patients with differentiated thyroid cancer requires a sufficiently stimulated serum concentration of TSH, for efficient uptake of radioiodine in thyroid tissue. The standard method to increase the serum TSH level is withdrawal of thyroid hormone therapy.

A preliminary study on the use of rhTSH before thyroid remnant ablation in 10 patients was published by Robbins et al. (121). In none of the patients who received a mean dose of 110 mCi (range 30-250 mCi) ^{131}I after pretreatment with rhTSH did a follow-up WBS 5-13 months later show any visible thyroid bed uptake. In a larger retrospective study by the same group (122), 38/45 (84%) of patients prepared by rhTSH (radioiodine dose 110 ± 65 mCi) and 34/42 (81%) of patients prepared by thyroid hormone withdrawal (radioiodine dose 129 ± 74 mCi) had complete resolution of visible thyroid bed uptake on follow-up diagnostic WBS.

Two prospective studies have been published in which it was assessed whether administration of rhTSH is useful as an adjunct to radioiodine for post-surgical ablation of thyroid remnants, using a low (30 mCi) standard dose of ^{131}I. In the study by Pacini et al. (123), the rate of ablation was prospectively compared between three groups of patients consecutively assigned to one of three treatment arms: in the first arm, patients (n = 50) were treated while hypothyroid, in the second arm, patients (n = 42) were treated while hypothyroid and stimulated in addition with rhTSH and in the third arm, patients (n = 70) were treated while euthyroid on L-thyroxine and stimulated with rhTSH. The outcome of thyroid ablation was assessed by a diagnostic WBS 72 h after administration of 4 mCi ^{131}I, performed in the hypothyroid state 6-10 months after ablation. The rate of successful ablation, defined as the disappearance of any visible uptake in the thyroid bed, was similar in the hypothyroid and hypothyroid/rhTSH-stimulated groups (84% and 78.5%, respectively). A significantly lower rate of ablation (54%) was achieved in the euthyroid, rhTSH-stimulated group. This study indicates that

when using rhTSH in patients on L-thyroxine therapy, a 30 mCi standard dose of ^{131}I is not sufficient for a satisfactory thyroid ablation rate. The authors mentioned as possible reasons for this failure a lower 24-h RAIU, a lower radiation dose delivered to the residues, and an accelerated iodine clearance in the group of patients on L-thyroxine therapy in comparison to the hypothyroid groups.

Barbaro et al. (124) compared the efficacy of thyroid remnant ablation in 16 patients who were treated with 30 mCi ^{131}I after rhTSH-stimulation, stopping L-thyroxine from the day before the first injection of rhTSH to the day after ^{131}I administration, with that in 24 comparable historical controls who were treated with 30 mCi ^{131}I in the hypothyroid state after L-thyroxine withdrawal. They hypothesized that iodine derived from L-thyroxine administered during the rhTSH-stimulated radioiodine ablation would interfere with radioiodine uptake causing a diminished effectiveness of the procedure. After 1 yr, all patients underwent a diagnostic WBS and serum Tg measurement using rhTSH. The percentage of successful ablation was 81% in patients pretreated with rhTSH and 75% in patients pretreated by L-T_4 withdrawal (not significant). None of the patients experienced symptoms of hypothyroidism during the 4 days of L-T_4 interruption, and serum T_4 remained in the normal range in the rhTSH-stimulated patients.

From these studies, it appears that rhTSH stimulated remnant ablation is a viable option. More studies, particularly employing larger ^{131}I doses, are required.

1.4.7 rhTSH as an adjunct to radioiodine therapy in differentiated thyroid cancer

Recombinant human TSH has been used on a compassionate need basis to prepare patients for radioiodine therapy. The first successful treatments of patients with differentiated metastatic thyroid cancer using ^{131}I after rhTSH stimulation were described in case reports (125-127). The reasons to use rhTSH instead of thyroid hormone withdrawal to prepare for the administration of a therapeutic dose of ^{131}I in these patients were earlier tumor growth after discontinuation of thyroid hormone therapy or inability to produce sufficient endogenous amounts of TSH when hypothyroid. Luster et al. (128) used rhTSH in conjunction with radioiodine therapy in 11 patients (16 treatments) with advanced differentiated thyroid cancer. Indications for the use of rhTSH in these patients included inability to tolerate withdrawal of thyroid hormones due to very poor physical condition and inability to achieve sufficiently high serum TSH levels after withdrawal. Ten patients had undergone thyroidectomy, and most had received prior radioablative therapy. Baseline Tg levels ranged from 25 to nearly 30,000 ng/mL. In 7 cases, post-therapy Tg levels assessed at 2 to 10 months after ^{131}I therapy had decreased by at least 30% compared to pre-therapy levels. After therapy, 3 patients showed marked clinical improvement, and/or decreased or stabilized tumor burden on WBS. Three

patients died of progressive disease within 2 months of therapy before follow-up assessments could be performed. No adverse events were reported among the 8 surviving patients. Lippi et al. (129) studied 12 patients who underwent ^{131}I treatment after rhTSH administration, while euthyroid on L-thyroxine. Nine underwent diagnostic WBS after two injections of 0.9 mg rhTSH. They then received identical rhTSH pretreatment to promote therapeutic ^{131}I uptake. Three patients received only rhTSH-pretreated ^{131}I therapy. Administration of rhTSH promoted ^{131}I uptake in all patients. Administration of rhTSH also caused a significant increase in serum Tg concentrations. According to measurements 3-12 months after therapy, serum Tg levels fell in 4, and stabilized in 2 out of 11 patients. RhTSH was well tolerated but individuals with bone metastases experienced transient pain and swelling. These results suggest that rhTSH administration offers a promising alternative to thyroid hormone withdrawal in radioiodine therapy. It has to be determined whether cessation of thyroid hormone for 3–5 days before the therapeutic dose of ^{131}I (in an attempt to reduce iodine intake) results in better retention of ^{131}I in the lesions (130). It is also important to determine the lowest dose of rhTSH that induces satisfactory uptake of therapy doses of ^{131}I, since TSH is a stimulus for thyroid tumor growth (131). Another question is whether rhTSH can enhance the efficacy of chemotherapy in differentiated thyroid cancer. A preliminary report from Santini et al. (132) suggests that the efficacy of chemotherapy for thyroid cancer metastases is increased if the tumor is stimulated by rhTSH. This study raises a new perspective for patients with metastatic thyroid cancer that does not concentrate ^{131}I, and who have few therapeutic options.

1·5

Outline of the Thesis

1·5

Outline of the Thesis

In this thesis the use of recombinant human thyrotropin (rhTSH) as a possible adjunct to radioiodine therapy for thyroid volume reduction in patients with nontoxic, nodular goiter is explored.

Chapter 2. Radioiodine (^{131}I) is increasingly used as treatment for volume reduction of nontoxic, nodular goiter. A high dose of ^{131}I is often needed because of low thyroid radioiodine uptake (RAIU). We investigated whether pretreatment with a single, low dose of rhTSH (Thyrogen®, Genzyme) enhances RAIU in 15 patients with nontoxic, nodular goiter. We observed that pretreatment with a single, low dose of rhTSH in patients with nontoxic, nodular goiter increased RAIU considerably. These observations hold promise that administration of rhTSH before ^{131}I therapy for nontoxic, nodular goiter will allow treatment with lower doses of ^{131}I in these patients.

In **chapter 3** we investigated whether rhTSH pretreatment induces changes in the regional distribution of radioiodine as visualized on thyroid scintigrams in these patients. We found that a single, low dose of rhTSH caused a more homogeneous distribution of radioiodine within the thyroid gland in patients with a nontoxic, nodular goiter by stimulating radioiodine uptake in relatively cold areas more than in relatively hot areas. This was most marked in patients with a low baseline serum TSH level. Our data suggest that pretreatment with rhTSH may improve the efficacy of radioiodine treatment for volume reduction of nodular goiters, especially in patients with a low baseline serum TSH level.

In patients with nodular goiter, ^{131}I therapy results in a mean reduction in thyroid volume of approximately 40% after 1 year. In **chapter 4** we studied the safety and efficacy of therapy with a reduced dose of ^{131}I after pretreatment with rhTSH. We demonstrated that pretreatment with a single, low dose of rhTSH allowed approximately 50–60% reduction of the therapeutic dose of radioiodine without compromising the efficacy of thyroid volume reduction.

Chapter 5 deals with the dosimetric aspects of therapy with a reduced dose of ^{131}I after pretreatment with rhTSH in patients with nontoxic, nodular goiter. ^{131}I therapy after pretreatment with a single, low dose of rhTSH, with the dose reduced according to the rhTSH-induced increase in 24-h RAIU, caused lower radiation-absorbed doses in extrathyroidal organs and tissues, especially bladder and stomach, and no significant increase in the release of ^{131}I-labeled thyroid hormones into the circulation of patients with nodular goiter. We concluded that this mode of therapy is promising, especially when the dose of radioiodine to be administered without rhTSH pretreatment is high.

In **chapter 6** we give a summary of the studies in this thesis and we outline the perspective of treatment of nontoxic, nodular goiter by radioiodine focusing on the role of pretreatment with rhTSH.

Finally **chapter 7** presents the summary and perspective in Dutch.

References

1 **Berghout A, Wiersinga WM, Smits NJ, Touber JL** 1990 Interrelationships between age, thyroid volume, thyroid nodularity, and thyroid function in patients with sporadic nontoxic goiter. Am J Med 89:602-608

2 **Singer PA, Cooper DS, Daniels GH, Ladenson PW, Greenspan FS, Levy EG, Braverman LE, Clark OH, McDougall IR, Ain KV, Dorfman SG** 1996 Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. American Thyroid Association. Arch Intern Med 156:2165-2172

3 **Mack E** 1995 Management of patients with substernal goiters. Surg Clin North Am 75:377-394

4 **Hegedüs L, Nygaard B, Hansen JM** 1999 Is routine thyroxine treatment to hinder postoperative recurrence of nontoxic goiter justified? J Clin Endocrinol Metab 84:756-760

5 **Ross DS** 1992 Thyroid hormone suppressive therapy of sporadic nontoxic goiter. Thyroid 2:263-269

6 **Berghout A, Wiersinga WM, Drexhage HA, Smits NJ, Touber JL** 1990 Comparison of placebo with L-thyroxine alone or with carbimazole for treatment of sporadic nontoxic goitre. Lancet 336:193-197

7 **Wesche MFT, Tiel-v Buul MMC, Lips P, Smits NJ, Wiersinga WM** 2001 A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. J Clin Endocrinol Metab 86:998-1005

8 **Toft AD** 1994 Thyroxine therapy. N Engl J Med 331:174-180

9 **Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY** 1996 Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. J Clin Endocrinol Metab 81:4278-4289

10 **Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D'Agostino RB** 1994 Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 331:1249-1252

11 **Biondi B, Fazio S, Carella C, Amato G, Cittadini A, Lupoli G, Sacca L, Bellastella A, Lombardi G** 1993 Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. J Clin Endocrinol Metab 77:334-338

12 **Ching GW, Franklyn JA, Stallard TJ, Daykin J, Sheppard MC, Gammage MD** 1996 Cardiac hypertrophy as a result of long-term thyroxine therapy and thyrotoxicosis. Heart 75:363-368

13 **Shapiro LE, Sievert R, Ong L, Ocampo EL, Chance RA, Lee M, Nanna M, Ferrick K, Surks MI** 1997 Minimal cardiac effects in asymptomatic athyreotic patients chronically treated with thyrotropin-suppressive doses of L-thyroxine. J Clin Endocrinol Metab 82:2592-2595

14 **Keiderling Von W, Emrich D, Hauswaldt Ch, Hoffmann G** 1964 Ergebnisse der Radiojod-Verkleinerungstherapie euthyreoter Strumen. Dtsch Med Wochenschr 89:453-457

15 **Frey KW** 1979 Früh- und Spätergebnisse der 131Jod-therapie der blanden Struma im Kropfendemiegebiet Südbayerns. Fortschr Röntgenstr 130:172-174

16 **Klein B, Klein E, Horster FA** 1989 Ergebnisse der fraktionierten Radiojodtherapie bei 696 Hyperthyreosen und 690 blanden Strumen. Nucl Med 28:129-136

17 **Kay TWH, d'Emden MC, Andrews JT, Martin FIR** 1988 Treatment of non-toxic multinodular goiter with radioactive iodine. Am J Med 84:19-22

18 **Verelst J, Bonnyns M, Glinoer D** 1990 Radioiodine therapy in voluminous multinodular non-toxic goitre. Acta Endocrinol (Copenh) 122:417-421

19 **Hegedüs L, Hansen BM, Knudsen N, Hansen JM** 1988 Reduction of size of thyroid with radioactive iodine in multinodular non-toxic goitre. BMJ 297:661-662

20 **Nygaard B, Hegedüs L, Gervil M, Hjalgrim H, Soe-Jensen P, Hansen JM** 1993 Radioiodine treatment of multinodular non-toxic goitre. BMJ 307:828-832

21 **Huysmans DAKC, Hermus ARMM, Corstens FHM, Barentsz JO, Kloppenborg PWC** 1994 Large, compressive goiters treated with radioiodine. Ann Intern Med 121:757-762

22 **Wesche MF, Tiel-v Buul MM, Smits NJ, Wiersinga WM** 1995 Reduction in goiter size by 131I therapy in patients with non-toxic multinodular goiter. Eur J Endocrinol 132:86-87

23 **de Klerk JM, Van Isselt JW, van Dijk A, Hakman ME, Pameijer FA, Koppeschaar HP, Zelissen PM, van Schaik JP, Van Rijk PP** 1997 Iodine-131 therapy in sporadic nontoxic goiter. J Nucl Med 38:372-376

24 **Bonnema SJ, Bertelsen H, Mortensen J, Andersen PB, Knudsen DU, Bastholt L, Hegedüs L** 1999 The feasibility of high dose iodine 131 treatment as an alternative to surgery in patients with a very large goiter: effect on thyroid function and size and pulmonary function. J Clin Endocrinol Metab 84:3636-3641

25 **Le Moli R, Wesche MF, Tiel-van Buul MM, Wiersinga WM** 1999 Determinants of longterm outcome of radioiodine therapy of sporadic non- toxic goitre. Clin Endocrinol (Oxf) 50:783-789

26 **Hegedüs L, Bennedbæk FN** 1997 Radioiodine for non-toxic diffuse goitre. Lancet 350:409-410

27 **Howarth DM, Epstein MT, Thomas PA, Allen LW, Akerman R, Lan L** 1997 Outpatient management of patients with large multinodular goitres treated with fractionated radioiodine. Eur J Nucl Med 24:1465-1469

28 **Nygaard B, Soes-Petersen U, Hoilund-Carlsen PF, Veje A, Holst PE, Vestergaard A, Solling K** 1996 Improvement of upper airway obstruction after 131I-treatment of multinodular nontoxic goiter evaluated by flow volume loop curves. J Endocrinol Invest 19:71-75

29 **Huysmans D, Hermus A, Edelbroek M, Barentsz J, Corstens F, Kloppenborg P** 1997 Radioiodine for nontoxic multinodular goiter. Thyroid 7:235-239

30 **Nygaard B, Faber J, Hegedüs L** 1994 Acute changes in thyroid volume and function following 131I therapy of multinodular goitre. Clin Endocrinol (Oxf) 41:715-718

31 **Nygaard B, Knudsen JH, Hegedüs L, Scient AV, Hansen JE** 1997 Thyrotropin receptor antibodies and Graves' disease, a side-effect of 131I treatment in patients with nontoxic goiter. J Clin Endocrinol Metab 82:2926-2930

32 **Huysmans DAKC, Hermus ARMM, Edelbroek MAL, Tjabbes T, Oostdijk, Ross HA, Corstens FHM, Kloppenborg PWC** 1997 Autoimmune hyperthyroidism occurring late after radioiodine treatment for volume reduction of large multinodular goiters. Thyroid 7:535-539

33 **Huysmans DAKC, Buijs WCAM, van de Ven MTP, van den Broek WJM, Kloppenborg PWC, Hermus ARMM, Corstens FHM** 1996 Dosimetry and risk estimates of radioiodine therapy for large, multinodular goiters. J Nucl Med 37:2072-2079

34 **Cohen RN, Weintraub BD, Wondisford FE** 2000 Thyrotropin. In: Braverman LE, Utiger RD (eds). Werner and Ingbar's The Thyroid. Lippincott, Williams & Wilkins, Philadelphia: 202-233

35 **Pierce JG, Parsons TF** 1981 Glycoprotein hormones: structure and function. Annu Rev Biochem 50:465-495

36 **Matzuk MM, Kornmeier CM, Whitfield GK, Kourides IA, Boime I** 1988 The glycoprotein alpha-subunit is critical for secretion and stability of the human thyrotropin beta-subunit. Mol Endocrinol 2:95-100

37 **Berman MI, Thomas CG, Jr., Manjunath P, Sairam MR, Nayfeh SN** 1985 The role of the carbohydrate moiety in thyrotropin action. Biochem Biophys Res Commun 133:680-687

38 **Szkudlinski MW, Thotakura NR, Weintraub BD** 1995 Subunit-specific functions of N-linked oligosaccharides in human thyrotropin: role of terminal residues of alpha- and beta-subunit oligosaccharides in metabolic clearance and bioactivity. Proc Natl Acad Sci U S A 92:9062-9066

39 **Grossmann M, Szkudlinski MW, Zeng H, Kraiem Z, Ji I, Tropea JE, Ji TH, Weintraub BD** 1995 Role of the carboxy-terminal residues of the alpha-subunit in the expression and bioactivity of human thyroid-stimulating hormone. Mol Endocrinol 9:948-958

40 **Grossmann M, Szkudlinski MW, Tropea JE, Bishop LA, Thotakura NR, Schofield PR, Weintraub BD** 1995 Expression of human thyrotropin in cell lines with different glycosylation patterns combined with mutagenesis of specific glycosylation sites. Characterization of a novel role for the oligosaccharides in the in vitro and in vivo bioactivity. J Biol Chem 270:29378-29385

41 **Szkudlinski MW, Grossmann M, Leitolf H, Weintraub BD** 2000 Human thyroid-stimulating hormone: structure-function analysis. Methods 21:67-81

42 **Petersen VB, McGregor AM, Belchetz PE, Elkeles RS, Hall R** 1978 The secretion of thyrotrophin with impaired biological activity in patients with hypothalamic-pituitary disease. Clin Endocrinol (Oxf) 8:397-402

43 **Faglia G, Bitensky L, Pinchera A, Ferrari C, Paracchi A, Beck-Peccoz P, Ambrosi B, Spada A** 1979 Thyrotropin secretion in patients with central hypothyroidism: evidence for reduced biological activity of immunoreactive thyrotropin. J Clin Endocrinol Metab 48:989-998

44 **Faglia G, Beck-Peccoz P, Ballabio M, Nava C** 1983 Excess of beta-subunit of thyrotropin (TSH) in patients with idiopathic central hypothyroidism due to the secretion of TSH with reduced biological activity. J Clin Endocrinol Metab 56:908-914

45 **Beck-Peccoz P, Amr S, Menezes-Ferreira MM, Faglia G, Weintraub BD** 1985 Decreased receptor binding of biologically inactive thyrotropin in central hypothyroidism. Effect of treatment with thyrotropin-releasing hormone. N Engl J Med 312:1085-1090

46 **Magner JA, Kane J, Chou ET** 1992 Intravenous thyrotropin (TSH)-releasing hormone releases human TSH that is structurally different from basal TSH. J Clin Endocrinol Metab 74:1306-1311

47 **Magner JA** 1990 Thyroid-stimulating hormone: biosynthesis, cell biology, and bioactivity. Endocr Rev 11:354-385

48 **Grossmann M, Weintraub BD, Szkudlinski MW** 1997 Novel insights into the molecular mechanisms of human thyrotropin action: structural, physiological, and therapeutic implications for the glycoprotein hormone family. Endocr Rev 18:476-501

49 **Szkudlinski MW, Fremont V, Ronin C, Weintraub BD** 2002 Thyroid-stimulating hormone and thyroid-stimulating hormone receptor structure-function relationships. Physiol Rev 82:473-502

50 **Paschke R, Ludgate M** 1997 The thyrotropin receptor in thyroid diseases. N Engl J Med 337:1675-1681

51 **Schaaf L, Leiprecht A, Saji M, Hubner U, Usadel KH, Kohn LD** 1997 Glycosylation variants of human TSH selectively activate signal transduction pathways. Mol Cell Endocrinol 132:185-194

52 **Reichert LE, Jr.** 1970 On the relationship between human thyrotrophin research standard A, the United States Pharmacopeia thyrotrophin standard (Bovine) and the International Standard for thyrotrophin (Bovine). J Clin Endocrinol Metab 31:331-333

53 **Uller RP, Van Herle AJ, Chopra IJ** 1973 Comparison of alterations in circulating thyroglobulin, triiodothyronine and thyroxine in response to exogenous (bovine) and endogenous (human) thyrotropin. J Clin Endocrinol Metab 37:741-745

54 **Uller RP, Van Herle AJ, Chopra IJ** 1977 Thyroidal response to graded doses of bovine thyrotropin. J Clin Endocrinol Metab 45:312-318

55 **Schneider PB, Robbins J, Condliffe PG** 1965 Thyroid response to human thyrotropin in man. J Clin Endocrinol Metab 25:514-517

56 **Snyder PJ, Utiger RD** 1972 Response to thyrotropin releasing hormone (TRH) in normal man. J Clin Endocrinol Metab 34:380-385

57 **Hays MT, Solomon DH, Pierce JG, Carstein ME** 1961 The effect of purified bovine thyroid-stimulating hormone in man. I. Dose-response characteristics studied with I-132. J Clin Endocrinol Metab 21:1469-1474

58 **Hershman JM, Edwards CL** 1972 Serum thyrotropin (TSH) levels after thyroid ablation compared with TSH levels after exogenous bovine TSH: implications for 131-I treatment of thyroid carcinoma. J Clin Endocrinol Metab 34:814-818

59 **Sherman WB, Werner SC** 1964 Generalized allergic reaction to bovine thyrotropin. JAMA 190:244-245

60 **Krishnamurthy GT** 1978 Human reaction to bovine TSH: concise communication. J Nucl Med 19:284-286

61 **Hays MT, Solomon DH, Werner SC** 1961 The effect of purified bovine thyroid-stimulating hormone in men. II. Loss of effectiveness with prolonged administration. J Clin Endocrinol Metab 21:1475-1482

62 **Hays MT, Solomon DH, Beall GN** 1967 Suppression of human thyroid function by antibodies to bovine thyrotropin. J Clin Endocrinol Metab 27:1540-1549

63 **Greenspan FS, Lowenstein JM, West MN, Okerlund MD** 1972 Immuno-reactive material to bovine TSH in plasma from patients with thyroid cancer. J Clin Endocrinol Metab 35:795-798

64 **Melmed S, Harada A, Hershman JM, Krishnamurthy GT, Blahd WH** 1980 Neutralizing antibodies to bovine thyrotropin in immunized patients with thyroid cancer. J Clin Endocrinol Metab 51:358-363

65 **Frohman LA, Baron MA, Schneider AB** 1982 Plasma immunoreactive TSH: spurious elevation due to antibodies to bovine TSH which cross-react with human TSH. Metabolism 31:834-840

66 **Greenspan FS, Lew W, Okerlund MD, Lowenstein JM** 1974 Falsely positive bovine TSH radioimmunoassay responses in sera from patients with thyroid cancer. J Clin Endocrinol Metab 38:1121-1122

67 **Sain A, Sham R, Singh A, Silver L** 1979 Erroneous thyroid-stimulating hormone radioimmunoassay results due to interfering antibovine thyroid-stimulating hormone antibodies. Am J Clin Pathol 71:540-542

68 **Law A, Jack GW, Tellez M, Edmonds CJ** 1986 In-vivo studies of a human-thyrotrophin preparation. J Endocrinol 110:375-378

69 **Brown P, Gajdusek DC, Gibbs CJ, Jr., Asher DM** 1985 Potential epidemic of Creutzfeldt-Jakob disease from human growth hormone therapy. N Engl J Med 313:728-731

70 **Hayashizaki Y, Miyai K, Kato K, Matsubara K** 1985 Molecular cloning of the human thyrotropin-beta subunit gene. FEBS Lett 188:394-400

71 **Wondisford FE, Radovick S, Moates JM, Usala SJ, Weintraub BD** 1988 Isolation and characterization of the human thyrotropin beta-subunit gene. Differences in gene structure and promoter function from murine species. J Biol Chem 263:12538-12542

72 **Watanabe S, Hayashizaki Y, Endo Y, Hirono M, Takimoto N, Tamaki M, Teraoka H, Miyai K, Matsubara K** 1987 Production of human thyroid-stimulating hormone in Chinese hamster ovary cells. Biochem Biophys Res Commun 149:1149-1155

73 **Wondisford FE, Usala SJ, DeCherney GS, Castren M, Radovick S, Gyves PW, Trempe JP, Kerfoot BP, Nikodem VM, Carter BJ** 1988 Cloning of the human thyrotropin beta-subunit gene and transient expression of biologically active human thyrotropin after gene transfection. Mol Endocrinol 2:32-39

74 **Szkudlinski MW, Thotakura NR, Bucci I, Joshi LR, Tsai A, East-Palmer J, Shiloach J, Weintraub BD** 1993 Purification and characterization of recombinant human thyrotropin (TSH) isoforms produced by Chinese hamster ovary cells: the role of sialylation and sulfation in TSH bioactivity. Endocrinology 133:1490-1503

75 **Thotakura NR, Szkudlinski MW, Weintraub BD** 1994 Structure-function studies of oligosaccharides of recombinant human thyrotrophin by sequential deglycosylation and resialylation. Glycobiology 4:525-533

76 **Huber GK, Fong P, Concepcion ES, Davies TF** 1991 Recombinant human thyroid-stimulating hormone: initial bioactivity assessment using human fetal thyroid cells. J Clin Endocrinol Metab 72:1328-1331

77 **Thotakura NR, Desai RK, Bates LG, Cole ES, Pratt BM, Weintraub BD** 1991 Biological activity and metabolic clearance of a recombinant human thyrotropin produced in Chinese hamster ovary cells. Endocrinology 128:341-348

78 **Cole ES, Lee K, Lauziere K, Kelton C, Chappel S, Weintraub B, Ferrara D, Peterson P, Bernasconi R, Edmunds T** 1993 Recombinant human thyroid stimulating hormone: development of a biotechnology product for detection of metastatic lesions of thyroid carcinoma. Biotechnology (NY) 11:1014-1024

79 **Szkudlinski MW, Thotakura NR, Tropea JE, Grossmann M, Weintraub BD** 1995 Asparagine-linked oligosaccharide structures determine clearance and organ distribution of pituitary and recombinant thyrotropin. Endocrinology 136:3325-3330

80 **Leitolf H, Szkudlinski MW, Hoang-Vu C, Thotakura NR, von zur MA, Brabant G, Weintraub BD** 1995 Effects of continuous and pulsatile administration of pituitary rat thyrotropin and recombinant human thyrotropin in a chronically cannulated rat. Horm Metab Res 27:173-178

81 **East-Palmer J, Szkudlinski MW, Lee J, Thotakura NR, Weintraub BD** 1995 A novel, nonradioactive in vivo bioassay of thyrotropin (TSH). Thyroid 5:55-59

82 **Colzani RM, Alex S, Fang SL, Braverman LE, Emerson CH** 1998 The effect of recombinant human thyrotropin (rhTSH) on thyroid function in mice and rats. Thyroid 8:797-801

83 **Braverman LE, Pratt BM, Ebner S, Longcope C** 1992 Recombinant human thyrotropin stimulates thyroid function and radioactive iodine uptake in the rhesus monkey. J Clin Endocrinol Metab 74:1135-1139

84 **Sauve F, Paradis M** 2000 Use of recombinant human thyroid-stimulating hormone for thyrotropin stimulation test in euthyroid dogs. Can Vet J 41:215-219

85 **Stegeman JR, Graham PA, Hauptman JG** 2003 Use of recombinant human thyroid-stimulating hormone for thyrotropin-stimulation testing of euthyroid cats. Am J Vet Res 64:149-152

86 **Ramirez L, Braverman LE, White B, Emerson CH** 1997 Recombinant human thyrotropin is a potent stimulator of thyroid function in normal subjects. J Clin Endocrinol Metab 82:2836-2839

87 **Torres MS, Ramirez L, Simkin PH, Braverman LE, Emerson CH** 2001 Effect of various doses of recombinant human thyrotropin on the thyroid radioactive iodine uptake and serum levels of thyroid hormones and thyroglobulin in normal subjects. J Clin Endocrinol Metab 86:1660-1664

88 **Lawrence JE, Emerson CH, Sullaway SL, Braverman LE** 2001 The effect of recombinant human tsh on the thyroid (123)i uptake in iodide treated normal subjects. J Clin Endocrinol Metab 86:437-440

89 **Nielsen VE, Bonnema SJ, Hegedüs L** 2004 Effects of 0.9 mg recombinant human thyrotropin on thyroid size and function in normal subjects: a randomized, double-blind, cross-over trial. J Clin Endocrinol Metab 89:2242-2247

90 **Schlumberger MJ** 1998 Papillary and follicular thyroid carcinoma. N Engl J Med 338:297-306

91 **Benua RS, Cicale NR, Sonenberg M, Rawson RW** 1962 The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. Am J Roentgenol Radium Ther Nucl Med 87:171-182

92 **Maxon HR, Thomas SR, Hertzberg VS, Kereiakes JG, Chen IW, Sperling MI, Saenger EL** 1983 Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. N Engl J Med 309:937-941

93 **DeGroot LJ, Kaplan EL, McCormick M, Straus FH** 1990 Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 71:414-424

94 **Solomon BL, Wartofsky L, Burman KD** 1996 Current trends in the management of well differentiated papillary thyroid carcinoma. J Clin Endocrinol Metab 81:333-339

95 **Mazzaferri EL, Kloos RT** 2001 Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 86:1447-1463

96 **Edmonds CJ, Hayes S, Kermode JC, Thompson BD** 1977 Measurement of serum TSH and thyroid hormones in the management of treatment of thyroid carcinoma with radioiodine. Br J Radiol 50:799-807

97 **Hilts SV, Hellman D, Anderson J, Woolfenden J, Van Antwerp J, Patton D** 1979 Serial TSH determination after T3 withdrawal or thyroidectomy in the therapy of thyroid carcinoma. J Nucl Med 20:928-932

98 **Goldman JM, Line BR, Aamodt RL, Robbins J** 1980 Influence of triiodothyronine withdrawal time on 131I uptake postthyroidectomy for thyroid cancer. J Clin Endocrinol Metab 50:734-739

99 **Dow KH, Ferrell BR, Anello C** 1997 Quality-of-life changes in patients with thyroid cancer after withdrawal of thyroid hormone therapy. Thyroid 7:613-619

100 **Meier CA, Braverman LE, Ebner SA, Veronikis I, Daniels GH, Ross DS, Deraska DJ, Davies TF, Valentine M, DeGroot LJ** 1994 Diagnostic use of recombinant human thyrotropin in patients with thyroid carcinoma (phase I/II study). J Clin Endocrinol Metab 78:188-196

101 **Ladenson PW, Braverman LE, Mazzaferri EL, Brucker-Davis F, Cooper DS, Garber JR, Wondisford FE, Davies TF, DeGroot LJ, Daniels GH, Ross DS, Weintraub BD** 1997 Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N Engl J Med 337:888-896

102 **Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, Cooper DS, Graham KE, Braverman LE, Skarulis MC, Davies TF, DeGroot LJ, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Becker DV, Maxon HR, III, Cavalieri RR, Spencer CA, McEllin K, Weintraub BD, Ridgway EC** 1999 A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J Clin Endocrinol Metab 84:3877-3885

103 **Robbins RJ, Tuttle RM, Sharaf RN, Larson SM, Robbins HK, Ghossein RA, Smith A, Drucker WD** 2001 Preparation by recombinant human thyrotropin or thyroid hormone withdrawal are comparable for the detection of residual differentiated thyroid carcinoma. J Clin Endocrinol Metab 86:619-625

104 **Cailleux AF, Baudin E, Travagli JP, Ricard M, Schlumberger M** 2000 Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? J Clin Endocrinol Metab 85:175-178

105 **Pacini F, Capezzone M, Elisei R, Ceccarelli C, Taddei D, Pinchera A** 2002 Diagnostic 131-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. J Clin Endocrinol Metab 87:1499-1501

106 **David A, Blotta A, Bondanelli M, Rossi R, Roti E, Braverman LE, Busutti L, degli Uberti EC** 2001 Serum thyroglobulin concentrations and (131)I whole-body scan results in patients with differentiated thyroid carcinoma after administration of recombinant human thyroid-stimulating hormone. J Nucl Med 42:1470-1475

107 **Pacini F, Molinaro E, Lippi F, Castagna MG, Agate L, Ceccarelli C, Taddei D, Elisei R, Capezzone M, Pinchera A** 2001 Prediction of disease status by recombinant human TSH-stimulated serum Tg in the postsurgical follow-up of differentiated thyroid carcinoma. J Clin Endocrinol Metab 86:5686-5690

108 **Haugen BR, Ridgway EC, McLaughlin BA, McDermott MT** 2002 Clinical comparison of whole-body radioiodine scan and serum thyroglobulin after stimulation with recombinant human thyrotropin. Thyroid 12:37-43

109 **Mazzaferri EL, Kloos RT** 2002 Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? J Clin Endocrinol Metab 87:1490-1498

110 **Robbins RJ, Chon JT, Fleisher M, Larson SM, Tuttle RM** 2002 Is the serum thyroglobulin response to recombinant human thyrotropin sufficient, by itself, to monitor for residual thyroid carcinoma? J Clin Endocrinol Metab 87:3242-3247

111 **Wartofsky L** 2002 Management of low-risk well-differentiated thyroid cancer based only on thyroglobulin measurement after recombinant human thyrotropin. Thyroid 12:583-590

112 **Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, Haugen BR, Sherman SI, Cooper DS, Braunstein GD, Lee S, Davies TF, Arafah BM, Ladenson PW, Pinchera A** 2003 A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 88:1433-1441

113 **Pacini F, Molinaro E, Castagna MG, Agate L, Elisei R, Ceccarelli C, Lippi F, Taddei D, Grasso L, Pinchera A** 2003 Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab 88:3668-3673

114 **Torlontano M, Crocetti U, D'Aloiso L, Bonfitto N, Di Giorgio A, Modoni S, Valle G, Frusciante V, Bisceglia M, Filetti S, Schlumberger M, Trischitta V** 2003 Serum thyroglobulin and 131I whole body scan after recombinant human TSH stimulation in the follow-up of low-risk patients with differentiated thyroid cancer. Eur J Endocrinol 148:19-24

115 **Schlumberger M, Berg G, Cohen O, Duntas L, Jamar F, Jarzab B, Limbert E, Lind P, Pacini F, Reiners C, Sanchez FF, Toft A, Wiersinga WM** 2004 Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. Eur J Endocrinol 150:105-112

116 **Wang W, Macapinlac H, Larson SM, Yeh SD, Akhurst T, Finn RD, Rosai J, Robbins RJ** 1999 [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography localizes residual thyroid cancer in patients with negative diagnostic (131)I whole body scans and elevated serum thyroglobulin levels. J Clin Endocrinol Metab 84:2291-2302

117 **Moog F, Linke R, Manthey N, Tiling R, Knesewitsch P, Tatsch K, Hahn K** 2000 Influence of thyroid-stimulating hormone levels on uptake of FDG in recurrent and metastatic differentiated thyroid carcinoma. J Nucl Med 41:1989-1995

118 **van Tol KM, Jager PL, Piers DA, Pruim J, de Vries EG, Dullaart RP, Links TP** 2002 Better yield of (18)fluorodeoxyglucose-positron emission tomography in patients with metastatic differentiated thyroid carcinoma during thyrotropin stimulation. Thyroid 12:381-387

119 **Petrich T, Borner AR, Otto D, Hofmann M, Knapp WH** 2002 Influence of rhTSH on [(18)F]fluorodeoxyglucose uptake by differentiated thyroid carcinoma. Eur J Nucl Med Mol Imaging 29:641-647

120 **Chin BB, Patel P, Cohade C, Ewertz M, Wahl R, Ladenson P** 2004 Recombinant human thyrotropin stimulation of fluoro-D-glucose positron emission tomography uptake in well-differentiated thyroid carcinoma. J Clin Endocrinol Metab 89:91-95

121 **Robbins RJ, Tuttle RM, Sonenberg M, Shaha A, Sharaf R, Robbins H, Fleisher M, Larson SM** 2001 Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin. Thyroid 11:865-869

122 **Robbins RJ, Larson SM, Sinha N, Shaha A, Divgi C, Pentlow KS, Ghossein R, Tuttle RM** 2002 A retrospective review of the effectiveness of recombinant human TSH as a preparation for radioiodine thyroid remnant ablation. J Nucl Med 43:1482-1488

123 **Pacini F, Molinaro E, Castagna MG, Lippi F, Ceccarelli C, Agate L, Elisei R, Pinchera A** 2002 Ablation of thyroid residues with 30 mCi (131)I: a comparison in thyroid cancer patients prepared with recombinant human TSH or thyroid hormone withdrawal. J Clin Endocrinol Metab 87:4063-4068

124 **Barbaro D, Boni G, Meucci G, Simi U, Lapi P, Orsini P, Pasquini C, Piazza F, Caciagli M, Mariani G** 2003 Radioiodine treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: effectiveness for postsurgical remnants ablation and possible role of iodine content in L-thyroxine in the outcome of ablation. J Clin Endocrinol Metab 88:4110-4115

125 **Rudavsky AZ, Freeman LM** 1997 Treatment of scan-negative, thyroglobulin-positive metastatic thyroid cancer using radioiodine 131I and recombinant human thyroid stimulating hormone. J Clin Endocrinol Metab 82:11-14

126 **Chiu AC, Delpassand ES, Sherman SI** 1997 Prognosis and treatment of brain metastases in thyroid carcinoma. J Clin Endocrinol Metab 82:3637-3642

127 **Robbins RJ, Voelker E, Wang W, Macapinlac HA, Larson SM** 2000 Compassionate use of recombinant human thyrotropin to facilitate radioiodine therapy: case report and review of literature. Endocr Pract 6:460-464

128 **Luster M, Lassmann M, Haenscheid H, Michalowski U, Incerti C, Reiners C** 2000 Use of recombinant human thyrotropin before radioiodine therapy in patients with advanced differentiated thyroid carcinoma. J Clin Endocrinol Metab 85:3640-3645

129 **Lippi F, Capezzone M, Angelini F, Taddei D, Molinaro E, Pinchera A, Pacini F** 2001 Radioiodine treatment of metastatic differentiated thyroid cancer in patients on L-thyroxine, using recombinant human TSH. Eur J Endocrinol 144:5-11

130 **Robbins RJ, Robbins AK** 2003 Clinical review 156: Recombinant human thyrotropin and thyroid cancer management. J Clin Endocrinol Metab 88:1933-1938

131 **Emerson CH, Colzani R, Braverman LE** 1997 Epithelial cell thyroid cancer and thyroid stimulating hormone--when less is more. J Clin Endocrinol Metab 82:9-10

132 **Santini F, Bottici V, Elisei R, Montanelli L, Mazzeo S, Basolo F, Pinchera A, Pacini F** 2002 Cytotoxic effects of carboplatinum and epirubicin in the setting of an elevated serum thyrotropin for advanced poorly differentiated thyroid cancer. J Clin Endocrinol Metab 87:4160-4165

chapter

2

2.1

Administration of a Single Low Dose of Recombinant Human Thyrotropin Significantly Enhances Thyroid Radioiodide Uptake in Nontoxic Nodular Goiter

Dyde A. Huysmans, Willy-Anne Nieuwlaat, Ronald J. Erdtsieck, Andries P. Schellekens, Jo W. Bus, Bert Bravenboer, and Ad R. Hermus

---

Departments of Nuclear Medicine (D.A.H., J.W.B.), Internal Medicine (B.B.), and Clinical Chemistry (A.P.S.), Catharina Hospital, Eindhoven; Department of Internal Medicine, Máxima Medical Center (R.J.E.), Veldhoven; Department of Endocrinology (W.-A.N., A.R.H.), Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

The Journal of Clinical Endocrinology & Metabolism 2000; 85(10):3592-3596

2.1

Abstract

Radioiodine (^{131}I) is increasingly used as treatment for volume reduction of nontoxic, nodular goiter. A high dose of ^{131}I is often needed because of low thyroid radioiodide uptake (RAIU). We investigated whether pretreatment with a single, low dose of recombinant human TSH (rhTSH; Thyrogen, Genzyme Transgenics Corp.) enhances RAIU in 15 patients with nontoxic, nodular goiter (14 women and 1 man; aged 61 ± 11 yr). Four patients were studied twice, and 1 patient was studied 3 times. RAIU was measured both under basal conditions and after pretreatment (im) with rhTSH, given either 2 h (0.01 mg; n = 7) or 24 h [0.01 mg (n = 7) or 0.03 mg (n = 7)] before ^{131}I administration (20–40 μCi). Serum levels of TSH, free T_4 (FT_4), and total T_3 were measured at 2, 5, 8, 24, 48, 72, 96, and 192 h after rhTSH administration.

After administration of 0.01 mg rhTSH, serum TSH rose from 0.7 ± 0.5 to a peak level of 4.4 ± 1.1 mU/L ($P < 0.0001$), FT_4 rose from 16.0 ± 2.6 to 18.5 ± 3.7 pmol/L ($P < 0.0001$), and T_3 rose from 2.10 ± 0.41 to 2.63 ± 0.66 nmol/L ($P < 0.0001$). After administration of 0.03 mg rhTSH, TSH rose from 0.6 ± 0.4 to 15.8 ± 2.3 mU/L ($P < 0.0001$), FT_4 rose from 15.2 ± 1.5 to 21.7 ± 2.9 pmol/L ($P < 0.0001$), and T_3 rose from 1.90 ± 0.43 to 3.19 ± 0.61 nmol/L ($P < 0.0001$). Peak TSH levels were reached at 5–8 h and peak FT_4 and T_3 levels at 8–96 h after rhTSH administration.

Administration of 0.01 mg rhTSH 2 h before ^{131}I increased 24-h RAIU from 30 ± 11% to 42 ± 10% ($P < 0.02$), 0.01 mg rhTSH administered 24 h before ^{131}I increased 24-h RAIU from 29 ± 10% to 51 ± 10% ($P < 0.0001$), and 0.03 mg rhTSH administered 24 h before ^{131}I increased 24-h RAIU from 33 ± 11% to 63 ± 9% ($P < 0.0001$). After administration of 0.01 mg rhTSH 2 h before ^{131}I, 24-h RAIU did not increase in 1 patient, whereas the increase in 24-h RAIU was less than 10% in 2 other patients. In contrast, administration of rhTSH 24 h before ^{131}I increased 24-h RAIU by more than 10% in all 14 patients (by >20% in 10 and by >30% in 6).

In conclusion, pretreatment with a single, low dose of rhTSH in patients with nontoxic, nodular goiter increased RAIU considerably. Our observations hold promise that administration of rhTSH before ^{131}I therapy for nontoxic, nodular goiter will allow treatment with lower doses of ^{131}I in these patients.

Introduction

A number of studies, using ultrasonography, computed tomography, or magnetic resonance imaging for accurate measurements of thyroid volume, have shown that radioiodine (^{131}I) therapy in patients with nontoxic, nodular goiter results in a mean reduction in thyroid volume of approximately 40% after 1 yr (1, 2, 3, 4, 5) and of 50–60% after 3–5 yr (2, 6, 7). In the majority of patients radioiodine treatment decreases not only thyroid volume, but also compressive symptoms (3). The improvement in compressive symptoms is accompanied by substantial tracheal widening, as measured by magnetic resonance imaging (3), and improvement in respiratory function (3, 8).

The amount of radioiodine administered depended on thyroid weight and radioactive iodide uptake (RAIU) in the thyroid in the reported studies. Doses of approximately 100 μCi [3.7 megabecquerels (MBq)] radioiodine/g thyroid tissue corrected for RAIU at 24 h were usually given. As patients with nontoxic, nodular goiter usually have a rather low RAIU, high doses of radioiodine are often needed, causing considerable irradiation of extrathyroidal organs and tissues (9). Therefore, it is of interest to explore strategies to enhance RAIU in these patients.

One of the causes of a low RAIU in patients with nontoxic, nodular goiter is the fact that the serum TSH level is in the low normal range or even below normal in most of these patients. It might be possible to enhance radioiodide uptake in patients with nontoxic, nodular goiter by pretreatment with either bovine TSH or human cadaver TSH. However, bovine TSH is no longer used in humans, because it frequently causes adverse reactions. Human cadaver TSH cannot be used in humans, because of the risk of development of Creutzfeld-Jacob disease.

Recently, recombinant human TSH (rhTSH) has become available for diagnostic use in patients with thyroid cancer. It has been shown that rhTSH stimulates ^{131}I uptake in thyroid remnants that persisted after thyroidectomy and in metastatic thyroid cancer, providing an alternative for thyroid hormone withdrawal for patients undergoing evaluation for thyroid cancer persistence and recurrence (10, 11).

A study in euthyroid mice and rats showed that ip administration of rhTSH (0.1 μg/g BW) given 3 h before administration of radioiodide did not increase RAIU (12). In mice, but not in rats, that were TSH suppressed by prior administration of T_3, a significant increase in RAIU was found (12). In two rhesus monkeys, im administration of 0.2 mg rhTSH given 5 h before radioiodide administration increased RAIU (by a factor of 1.85) in only one monkey (13). Administration of 0.2 mg rhTSH on 3 consecutive days in two other monkeys resulted in a doubling of RAIU in both monkeys (13).

To date, no observations have been reported on the influence of rhTSH administration on RAIU in healthy human subjects or patients with benign thyroid diseases. In the present study we investigated whether the administration of a single low dose of rhTSH enhances RAIU in patients with nontoxic, nodular goiter. If so, administration of rhTSH before ^{131}I therapy for nontoxic, nodular goiter holds promise in allowing treatment with lower doses of ^{131}I in these patients.

Subjects and Methods

Patients

Fifteen patients, 14 women and 1 man, aged 61 ± 11 yr (mean ± SD; range, 44–73 yr), referred for radioiodine therapy for volume reduction of nontoxic, nodular goiter, were studied. Four patients were studied twice, and 1 patient was studied 3 times. The mean thyroid weight, as estimated from planar thyroid scintigraphy, was 181 ± 77 g (range, 60–300 g). All patients had normal serum levels of free T_4 (FT_4; chemiluminescent immunoassay; ACS:180 FrT4, Chiron Corp., Fernwald, Germany; normal values in our laboratory, 9.0–22.3 pmol/L) and total T_3 (chemiluminescent immunoassay; ACS T3, Ciba Diagnostics Corp., Medfield MA; normal values in our laboratory, 1.0–3.0 nmol/L), whereas the serum TSH level was normal (n = 12 patients) or below normal (n = 3 patients; two-site chemiluminometric immunoassay; ACS TSH-3, Ciba Diagnostics Corp.; normal values in our laboratory, 0.2–5.5 mU/L). Based on the results of careful palpation of the thyroid followed by fine needle aspiration biopsy of dominant nodules and of those that had a different consistency from other nodules within the gland, there was no suspicion of thyroid cancer in any of the patients. None of the patients had a history of significant cardiopulmonary disease or a recent history of taking any medications known to affect thyroid function or to interfere with hormone measurements or RAIU. None of the patients had received iodine-containing agents in the last 6 months. An electrocardiogram, complete blood count, liver enzyme determinations, plasma creatinine and glucose measurements, and screening urinalysis did not show abnormalities in any of the patients. The study was approved by the institutional human research committee. Written informed consent was obtained from all patients.

Baseline investigations

On the day before radioiodide administration, 24-h urine was collected for measurement of iodide and creatinine excretion. Iodide excretion was 163 ± 46 μg/24 h (range, 102–273 μg/24 h). Immediately before radioiodide administration, blood was drawn for measurements of serum FT_4, T_3, and TSH. A diagnostic dose of 20 μCi (0.8 MBq) sodium (^{131}I) iodide was administered as an oral solution [together with 1 mCi (40 MBq) sodium (^{123}I) iodide for thyroid scintigraphy]. RAIU as a percentage of the administered dose of ^{131}I, corrected for physical decay, was measured at 3, 6, 24, 48, 72, and 168 h, using a 3 x 3-in. NaI(Tl) detector. Deadtime corrections were made using standard software. The use of the net area under the 364-keV peak of ^{131}I was checked to prohibit any interference of the low energy photons of ^{123}I with RAIU measurements. Thyroid scintigraphy in the 159-keV window of ^{123}I was performed 24 h after radioiodide administration (results not included in the present report).

Investigations with rhTSH

The influence of rhTSH on thyroid hormone levels and RAIU was investigated in each patient at least 2 weeks after radioiodide administration for the baseline investigations. On the day before the administration of rhTSH, 24-h urine was collected for measurements of iodide and creatinine excretion. Iodide excretion was 177 ± 48 μg/24 h (range, 112–265 μg/24 h). Immediately before the administration of rhTSH, blood was drawn for measurement of serum FT_4, T_3, and TSH. After reconstitution of freeze-dried rhTSH (ampoules containing 0.9 mg rhTSH; Thyrogen, Genzyme Transgenics Corp., Cambridge, MA) with 1.2 mL sterile water, part of the obtained solution was diluted with saline to a final concentration of 0.05 mg/mL. Immediately after dilution, 0.01 mg (0.2 mL; n = 14) or 0.03 mg (0.6 mL; n = 7) rhTSH was injected im in the quadriceps muscle. Vital signs (blood pressure, pulse rate, and body temperature) were recorded, and blood was drawn for measurement of serum FT_4, T_3, and TSH 2, 5, 8, 24, 48, 72, 96, and 192 h after administration of rhTSH. A diagnostic dose of 20–40 μCi (0.8–1.6 MBq) sodium ^{131}I was administered as an oral solution [together with 1 mCi (40 MBq) sodium ^{123}I for thyroid scintigraphy] either 2 h after the administration of rhTSH (0.01 mg; n = 7) or 24 h after the administration of rhTSH [0.01 mg (n = 7) or 0.03 mg (n = 7)]. RAIU as a percentage of the administered dose of ^{131}I, corrected for background activity from the radioiodine from the baseline investigation and for physical decay, was measured at 3, 6, 24, 48, 72, and 168 h. Thyroid scintigraphy was performed 24 h after radioiodide administration (results not included in the present report).

Statistical analyses

The mean ± SD are given. Statistical analyses were performed using the Mann-Whitney U test for unpaired observations (*P* values denoted as *P*), the Wilcoxon sign-rank test for paired observations (*P* values denoted as *P**), and the Spearman rank correlation test (*P* values denoted as *P***). The level of significance was 0.05.

Results

No symptoms and signs of thyrotoxicosis or other adverse effects were observed after rhTSH administration, and blood pressure, pulse rate and body temperature did not change (P^* > 0.05 at all time points compared to values immediately before rhTSH administration).

Effect of rhTSH administration on serum TSH, FT_4, and T_3 levels

After 0.01 mg rhTSH, serum TSH rose from 0.7 ± 0.5 mU/L (range, <0.03 to 1.7 mU/L) to a peak of 4.4 ± 1.1 mU/L (range, 2.2–6.3 mU/L; P^* < 0.0001). After 0.03 mg rhTSH, TSH rose from 0.6 ± 0.4 mU/L (range, < 0.03–1.2 mU/L) to a peak of 15.8 ± 2.3 mU/L (range, 13.6–20.0 mU/L; P^* < 0.0001). Peak TSH levels were reached at 5–8 h after administration of either dose of rhTSH (Fig. 1). Thereafter, TSH declined rapidly, and in all patients a transient decrease in serum TSH below the baseline level was observed. One week after rhTSH administration, TSH levels did not differ significantly from baseline levels in both groups of patients.

After 0.01 mg rhTSH, serum FT_4 rose from 16.0 ± 2.6 pmol/L (range, 12.6–20.7 pmol/L) to a peak of 18.5 ± 3.7 pmol/L (range, 14.1–26.7 pmol/L; P^* < 0.0001), and T_3 rose from 2.10 ± 0.41 nmol/L (range, 1.60–2.90 nmol/L) to a peak of 2.63 ± 0.66 nmol/L (range, 1.90–3.80 nmol/L; P^* < 0.0001). After 1 week, FT_4 and T_3 had returned to baseline levels. After 0.03 mg rhTSH, FT_4 rose from 15.2 ± 1.5 pmol/L (range, 13.9–17.3 pmol/L) to a peak of 21.7 ± 2.9 pmol/L (range, 18.7–26.6 pmol/L; P^* < 0.0001), and T_3 rose from 1.90 ± 0.43 nmol/L (range, 1.40–2.70 nmol/L) to a peak of 3.19 ± 0.61 nmol/L (range, 2.30–3.90 nmol/L; P^* < 0.0001). After 1 week, serum FT_4 (17.5 ± 3.2 pmol/L; range, 14.4–22.4 pmol/L) and T_3 (2.01 ± 0.43 nmol/L; range, 1.50–2.80 nmol/L) were still significantly above baseline levels (P^* < 0.0001). Peak levels of FT_4 occurred 8–96 h, and peak T_3 levels occurred 5–96 h after administration of rhTSH. Increases in TSH and FT_4 levels (*i.e.* peak level minus baseline level) were significantly larger in the patients who received 0.03 mg rhTSH than in the patients who received 0.01 mg rhTSH (P < 0.0001).

Effect of rhTSH administration on RAIU (Table 1)

Administration of 0.01 mg rhTSH 2 h before ^{131}I increased 24-h RAIU from 30 ± 11% to 42 ± 10% (P^* < 0.02); 0.01 mg rhTSH administered 24 h before ^{131}I increased 24-h RAIU from 29 ± 10% to 51 ± 10% (P^* < 0.0001), and 0.03 mg rhTSH administered 24 h before ^{131}I increased 24-h RAIU from 33 ± 11% to 63 ± 9% (P^* < 0.0001).

The ratio between 24-h RAIU after rhTSH and baseline 24-h RAIU was 1.5 ± 0.5 (range, 1.0–2.4) in patients who received 0.01 mg rhTSH 2 h before radioiodide, 1.9 ± 0.5 (range, 1.2–2.7) in those who received 0.01 mg rhTSH 24 h before radioiodide, and 2.0 ± 0.5 (range, 1.4–2.6) in those who received 0.03 mg rhTSH 24 h before

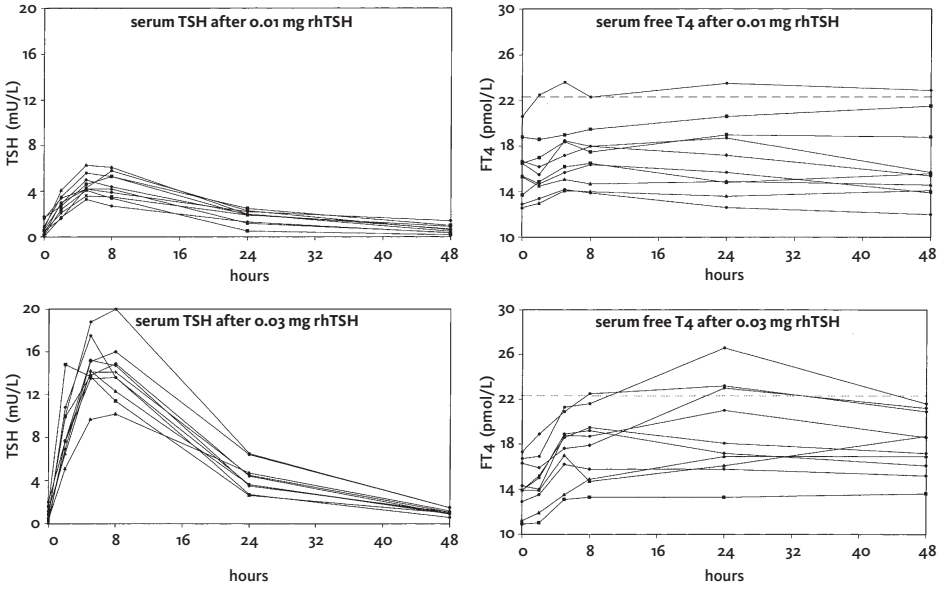


Figure 1. *Serum TSH levels (left panels) and FT_4 levels (right panels) before (0 h) and after im administration of 0.01 mg (upper panels) and 0.03 mg (lower panels) rhTSH in 15 patients with nontoxic, nodular goiter. rhTSH was administered immediately after blood withdrawal at 0 h. The dotted line indicates the upper level of the normal range for serum FT_4.*

Table 1. *Thyroid radioactive iodide uptake (RAIU; mean ± 1 SD) at 3, 6, and 24 h in the baseline investigation (without rhTSH administration) and in the investigation after rhTSH administration*

	0.01 mg rhTSH 2 h before radioiodine	0.01 mg rhTHS 24 h before radioiodine	0.03 mg rhTSH 24 h before radioiodine
3-h RAIU without rhTSH (%)	11 ± 4	12 ± 5	13 ± 4
3-h RAIU after rhTSH (%)	14 ± 6	32 ± 10	35 ± 8
Ratio	1.3 ± 0.5	2.6 ± 0.5	2.8 ± 0.8
6-h RAIU without rhTSH (%)	17 ± 6	18 ± 8	20 ± 6
6-h RAIU after rhTSH (%)	23 ± 8	40 ± 10	44 ± 11
Ratio	1.4 ± 0.4	2.4 ± 0.5	2.4 ± 0.9
24-h RAIU without rhTSH (%)	30 ± 11	29 ± 10	33 ± 11
24-h RAIU after rhTSH (%)	42 ± 10	51 ± 10	63 ± 9
Ratio	1.5 ± 0.5	1.9 ± 0.5	2.0 ± 0.5

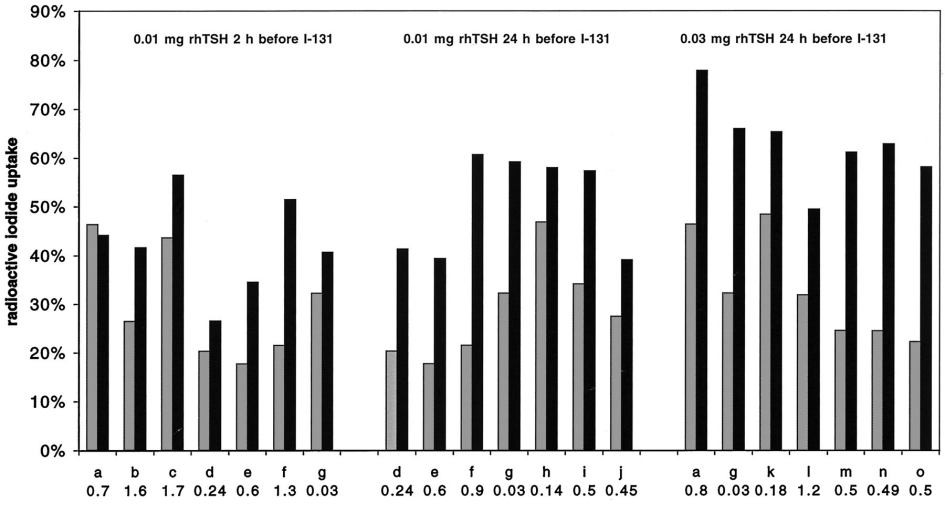


Figure 2. *Baseline 24-h radioactive iodide uptake (□) and 24-h radioactive iodide uptake after administration of recombinant human TSH (■) in 15 patients with nontoxic, nodular goiter. Patients are identified at the bottom of the figure as a to o. Four patients (a, d, e, and f) were studied twice; one patient (g) was studied 3 times. Serum TSH levels (milliunits per L) immediately before administration of rhTSH are also given at the bottom of the figure.*

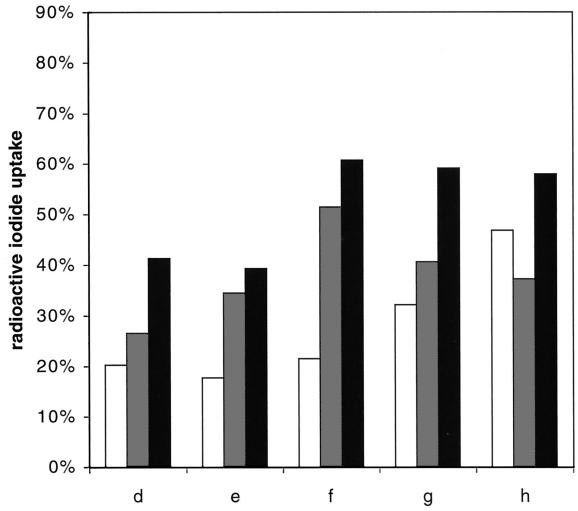


Figure 3. *Twenty-four-hour radioactive iodide uptake in 5 patients with nontoxic, nodular goiter, in whom rhTSH was given at 2 and 24 h before radioiodide administration on two different occasions. □, Baseline 24-h radioactive iodide uptake; □, 24-h radioactive iodide uptake after 0.01 mg rhTSH given 2 h before radioiodide; ■, 24-h radioactive iodide uptake after 0.01 mg rhTSH given 24 h before radioiodide.*

radioiodide ($P < 0.003$, 0.01 mg rhTSH 2 h before radioiodide *vs.* 0.03 mg rhTSH 24 h before radioiodide).

The ratio between 24-h RAIU after rhTSH and baseline 24-h RAIU showed a significant inverse correlation with baseline 24-h RAIU ($r = -0.79$; $P^{**} < 0.04$ for patients who received 0.01 mg rhTSH 2 or 24 h before radioiodide and $r = -0.89$; $P^{**} < 0.007$ for patients who received 0.03 mg rhTSH). The ratio between 24-h RAIU after rhTSH and baseline 24-h RAIU was not significantly correlated with the baseline TSH level.

The biological half-time of radioiodine in the thyroid, as estimated from the RAIU values of time points 48–168 h after the administration of radioiodide, was 61.3 ± 27.3 days in the baseline investigation and 56.6 ± 31.4 days in the investigation after rhTSH (P^* = NS).

Baseline 24-h RAIU and 24-h RAIU after rhTSH in individual patients are shown (Fig. 2). Of note, after administration of 0.01 mg rhTSH 2 h before ^{131}I, 24-h RAIU did not increase in 1 patient, whereas the increase in 24-h RAIU was less than 10% in 2 other patients. In contrast, administration of rhTSH 24 h before ^{131}I increased 24-h RAIU by more than 10% in all 14 patients (by >20% in 10 and by >30% in 6).

Individual values of 24-h RAIU are shown in five patients who received 0.01 mg rhTSH both 2 and 24 h before radioiodide on different occasions (Fig. 3). The ratio between 24-h RAIU after rhTSH and baseline 24-h RAIU was significantly higher for the 24-h interval between rhTSH and radioiodide administration than for the 2-h interval ($P^* < 0.0001$).

Discussion

It has been convincingly demonstrated that administration of rhTSH increases RAIU in thyroid remnants and thyroid cancer metastases (10, 11). However, to date there are no observations on the effects of administration of rhTSH on RAIU in benign thyroid diseases. In the present study we demonstrate that a single im injection of rhTSH given 24 h before radioiodide administration doubled RAIU in patients with nontoxic, nodular goiter. Our study was performed in an area with borderline sufficient iodine intake, where further restriction of iodine intake did not result in any significant enhancement of RAIU (Huysmans, D. A., *et al.*, unpublished observations).

The doubling of RAIU was reached by the use of remarkably low doses of rhTSH (0.01 or 0.03 mg). For comparison, a single im injection of 0.1 mg rhTSH was used in a study of the effects of rhTSH on serum thyroid hormone levels in six normal volunteers (14), whereas im injections of 0.9 mg rhTSH were used in two phase 3 studies in patients with thyroid cancer (10, 11). Accordingly, we found considerably lower peak levels of TSH (4.4 ± 1.1 mU/L after 0.01 mg rhTSH and 15.8 ± 2.3 mU/L after 0.03 mg rhTSH) than observed in normal volunteers after 0.1 mg rhTSH (50.9 ± 22.8 mU/L) (14) and in thyroid cancer patients after 0.9 mg rhTSH (101 ± 60 mU/L) (10).

In our study, the interval between the administration of rhTSH and radioiodide appeared to be an important factor for increasing RAIU; a 24-h interval between rhTSH administration and radioiodide administration was significantly more effective than a 2-hinterval. This finding is in accordance with the results of *in vitro* studies using FRTL-5 cells (15, 16). Weiss *et al.* (15) demonstrated that 12–24 h were needed for the onset of stimulation of iodide transport by a purified preparation of TSH. Kogai *et al.* (16) demonstrated that rhTSH (1 mU/mL) increased iodide-125 uptake only after 12 h of incubation, reaching a maximum after an incubation period of 72 h.

Iodide uptake across the basolateral membrane of thyroid follicular cells is catalyzed by the Na^+/I^- symporter (NIS). Immunohistochemical studies have demonstrated that under normal conditions, there is only limited expression of the Na^+/I^- symporter in the plasma membrane of thyroid follicular cells (17, 18). Kogai *et al.* (16) have shown that in FRTL-5 cells rhTSH induces a significant increase in NIS messenger ribonucleic acid at 3–6 h, reaching a maximum at 24 h. NIS protein levels were significantly increased only after 36 h, reaching a maximum at 72 h. Thus, optimal expression and/or activation of the Na^+/I^- symporter may take some time, which might explain our observation that a 24-h interval between rhTSH adminis-

tration and radioiodide administration was significantly more effective in increasing RAIU than a 2-h interval.

We found that the effects of administration of 0.03 and 0.01 mg rhTSH on RAIU were not significantly different. In contrast, 0.03 mg rhTSH caused a significantly greater maximal increase in serum thyroid hormone levels (42% increase in FT_4, 69% increase in T_3) than did 0.01 mg rhTSH (15% increase in FT_4, 25% increase in T_3). In only 8 of 21 observations was serum FT_4 and/or T_3 increased beyond the normal range after rhTSH administration, and in none of the patients were symptoms or signs of thyrotoxicosis (or any other side-effect) observed. For comparison, the increases in serum thyroid hormone levels after either dose of rhTSH appeared to be less than those found in normal volunteers after the administration of 0.1 mg rhTSH (54% increase in total T_4 and 89% increase in total T_3) (14).

No adverse effects of the administration of a single low dose of rhTSH were observed in our study. However, before rhTSH can be advised as an adjunct to radioiodine therapy in patients with nontoxic, nodular goiter, the safety of the administration of a therapeutic dose of radioiodine after pretreatment with rhTSH has to be investigated thoroughly. First, it has to be determined that pretreatment with rhTSH does not exacerbate the mild increases in serum thyroid hormone levels and thyroid volume commonly seen after radioiodine treatment of nontoxic, nodular goiter (19). Second, it has to be shown that administration of rhTSH before radioiodine therapy does not induce a rapid release of ^{131}I-labeled thyroid hormones and/or thyroglobulin from the thyroid into the circulation, thereby increasing total body irradiation.

Our observations hold promise for rhTSH as an adjunct to radioiodine treatment for thyroid volume reduction in patients with nontoxic, nodular goiter, as it may allow treatment with lower doses of ^{131}I. Furthermore, the administration of rhTSH may alter the distribution of radioiodine within the thyroid gland, which may be particularly advantageous if it enhances the uptake of radioiodide in cold areas. Our study was performed in an area with borderline sufficient iodine intake. The effect of rhTSH pretreatment on RAIU may be even greater in areas with a higher iodine intake. However, randomized studies comparing the efficacies of radioiodine therapies with and without rhTSH pretreatment need to be performed before its use can be advised.

References

1 **Hegedüs L, Hansen BM, Knudsen N, Hansen JM** 1988 Reduction of size of thyroid with radioactive iodine in multinodular non-toxic goitre. Br Med J 297:661–662

2 **Nygaard B, Hegedüs L, Gervil M, Hjalgrim H, Søe-Jensen P, Hansen JM** 1993 Radioiodine treatment of multinodular non-toxic goitre. Br Med J 307:828–832

3 **Huysmans DAKC, Hermus ARMM, Corstens FHM, Barentsz JO, Kloppenborg PWC** 1994 Large, compressive goiters treated with radioiodine. Ann Intern Med 121:757–762

4 **Wesche MF, Tiel-van Buul MM, Smits NJ, Wiersinga WM** 1995 Reduction in goiter size by ^{131}I therapy in patients with non-toxic multinodular goiter. Eur J Endocrinol 132:86–87

5 **de Klerk JM, van Isselt JW, van Dijk A, et al.** 1997 Iodine-131 therapy in sporadic non-toxic goiter. J Nucl Med 38:372–376

6 **Huysmans D, Hermus A, Edelbroek M, Barentsz J, Corstens F, Kloppenborg P** 1997 Radioiodine for nontoxic multinodular goiter. Thyroid 7:235–239

7 **Hermus AR, Huysmans DA** 1998 Treatment of benign nodular thyroid disease. N Engl J Med 338:1438–1447

8 **Nygaard B, Soes-Petersen U, Hoilund-Carlsen PF, et al.** 1996 Improvement of upper airway obstruction after ^{131}I-treatment of multinodular nontoxic goiter evaluated by flow volume loop curves. J Endocrinol Invest 19:71–75

9 **Huysmans DAKC, Buijs WCAM, van de Ven MTJ, et al.** 1996 Dosimetry and risk estimates of radioiodine therapy for large, multinodular goiters. J Nucl Med 37:2072–2079

10 **Ladenson PW, Braverman LE, Mazzaferri EL, et al.** 1997 Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N Engl J Med 337:888–896

11 **Haugen BR, Pacini F, Reiners C, et al.** 1999 A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J Clin Endocrinol Metab 84:3877–3885

12 **Colzani RM, Alex S, Fang SL, Braverman LE, Emerson CH** 1998 The effect of recombinant human thyrotropin (rhTSH) on thyroid function in mice and rats. Thyroid 8:797–801

13 **Braverman LE, Pratt BM, Ebner S, Longcope C** 1992 Recombinant human thyrotropin stimulates thyroid function and radioactive iodine uptake in the rhesus monkey. J Clin Endocrinol Metab 74:1135–1139

14 **Ramirez L, Braverman LE, White B, Emerson CH** 1997 Recombinant human thyrotropin is a potent stimulator of thyroid function in normal subjects. J Clin Endocrinol Metab 82:2836–2839

15 **Weiss SJ, Philp NJ, Ambesi-Impiombato FS, Grollman EF** 1984 Thyrotropin-stimulated iodide transport mediated by adenosine 3',5'-monophosphate and dependent on protein synthesis. Endocrinology 114:1099–1107

16 **Kogai T, Endo T, Saito T, Miyazaki A, Kawaguchi A, Onaya T** 1997 Regulation by thyroid-stimulating hormone of sodium/iodide symporter gene expression and protein levels in FRTL-5 cells. Endocrinology 138:2227–2232

17 **Jhiang SM, Cho JY, Ryu KY, et al.** 1998 An immunohistochemical study of Na^+/I^- symporter in human thyroid tissues and salivary gland tissues. Endocrinology 139:4416–4419

18 **Caillou B, Troalen F, Baudin E, et al.** 1998 Na^+/I^- symporter distribution in human thyroid tissues: an immunohistochemical study. J Clin Endocrinol Metab 83:4102–4106

19 **Nygaard B, Faber J, Hegedüs L** 1994 Acute changes in thyroid volume and function following ^{131}I therapy of multinodular goitre. Clin Endocrinol (Oxf) 41:715–718

2.2

Addendum

2.2

Addendum

In the study reported in **chapter 2.1** we found that the interval between the administration of rhTSH and radioiodine was an important factor for increasing radioactive iodine uptake (RAIU): a 24-h interval between rhTSH administration and radioiodine administration was significantly more effective than a 2-h interval. Iodine uptake across the basolateral membrane of thyroid follicular cells is catalyzed by the Na^+/I^- symporter (NIS). Stimulation of NIS mRNA levels (and stimulation of NIS protein levels and translocation of the NIS protein to the basolateral membrane) by rhTSH may take some time, which might explain our observation. The figure shows results of a pilot experiment we performed in mice. RhTSH administration increased NIS mRNA levels 5-fold with peak levels reached after 9 hours. This observation in mice is in line with our hypothesis.

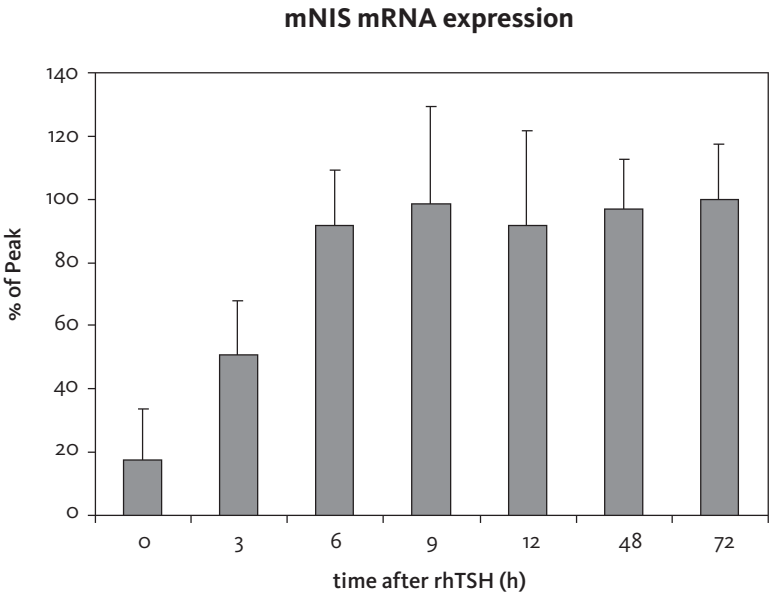


Figure. *Effect of rhTSH administration on NIS mRNA expression in mice. Twenty-one mice received 3 µg rhTSH iv and after 0, 3, 6, 9, 12, 48, or 72 hours they were killed (3 mice per time point), their thyroids removed and frozen at -80 °C. The thyroids were homogenized to measure mouse (m)NIS mRNA levels (courtesy to Dr. J.W. Smit, Leiden University Medical Center, Leiden, The Netherlands).*

chapter

3

3.1

Pretreatment with Recombinant Human TSH Changes the Regional Distribution of Radioiodine on Thyroid Scintigrams of Nodular Goiters

Willy-Anne Nieuwlaat, Ad R. Hermus,
Ferida Sivro-Prndelj, Frans H. Corstens,
and Dyde A. Huysmans

Department of Nuclear Medicine (W.-A.N., F.S.-P., D.A.H.),
Catharina Hospital, Eindhoven;
Departments of Endocrinology (W.-A.N., A.R.H.) and Nuclear Medicine
(F.H.C.), Radboud University Nijmegen Medical Center, Nijmegen,
The Netherlands

The Journal of Clinical Endocrinology & Metabolism 2001; 86(11):5330-5336

3.1

Abstract

In a recent study, we demonstrated that pretreatment with a single, low dose of recombinant human TSH (rhTSH) doubles 24-h thyroid radioactive iodine uptake in patients with nodular goiter. The purpose of the present study was to investigate whether rhTSH pretreatment induces changes in the regional distribution of radioiodine as visualized on thyroid scintigrams in these patients.

Anterior planar thyroid ^{123}I scintigrams were obtained in 26 patients with a nodular goiter (23 women and 3 men; age, 62 ± 9 yr, mean ± SD; thyroid weight, 165 ± 72 g) 24 h after administration of a diagnostic dose of radioiodine. All patients were studied twice: first, without rhTSH pretreatment (baseline study), and second, after an im injection of 0.01 mg (n = 10) or 0.03 mg rhTSH (n = 16), given 24 h before radioiodine administration (rhTSH study). For quantification of regional differences in radioiodine uptake, a region of interest method was used.

Upon visual inspection, baseline scintigrams showed a heterogeneous uptake of radioiodine. In general, rhTSH scintigrams also showed heterogeneous radioiodine uptake. In some patients, the distribution of radioiodine in the rhTSH scintigram was considerably more homogeneous than in the baseline scintigram. In a few patients, originally "cold" areas had changed into "hot" ones, whereas originally hot areas had changed into cold ones. Quantification of regional radioiodine uptake showed that pretreatment with rhTSH caused a larger increase in radioiodine uptake in relatively cold areas and a smaller increase in radioiodine uptake in relatively hot areas, compared with the increase in radioiodine uptake in the entire thyroid. In patients with a baseline serum TSH level of 0.5 mU/liter or lower, the increase in radioiodine uptake in relatively cold areas was significantly larger than in patients with a baseline serum TSH level higher than 0.5 mU/liter.

In conclusion, a single, low dose of rhTSH not only doubled 24-h radioactive iodine uptake but also caused a more homogeneous distribution of radioiodine within the thyroid gland in patients with a nodular goiter by stimulating radioiodine uptake in relatively cold areas more than in relatively hot areas. This was most marked in patients with a low baseline serum TSH level. Our data suggest that pretreatment with rhTSH may improve the efficacy of radioiodine treatment for volume reduction of nodular goiters, especially in patients with a low baseline serum TSH level.

Introduction

Radioiodine treatment is effective in reducing thyroid volume in most patients with nontoxic, nodular goiter. In a number of reports in which ultrasonography, computed tomography, or magnetic resonance imaging for accurate measurements of thyroid volume were used, decreases in goiter size of approximately 40%, on average, after 1 yr, (1, 2, 3, 4, 5, 6) and of 50–60% after 3–5 yr have been described (2, 7, 8). In most patients, compressive symptoms improved as well (3). The improvement in compressive symptoms was accompanied by significant tracheal widening, as measured by magnetic resonance imaging (3), and improvement in respiratory function (3, 9).

In the reported studies, a single dose of approximately 100 μCi (3.7 MBq) of ^{131}I per gram of thyroid tissue corrected for radioactive iodine uptake (RAIU) at 24 h was given. In patients with nontoxic, nodular goiter, RAIU is usually rather low. As a result, high doses of ^{131}I are often needed, causing a relatively high radiation burden to extrathyroidal tissues (10). One of the causes of a low RAIU in these patients is a low-normal or below normal serum level of TSH.

In the last few years, recombinant human TSH (rhTSH) has become available for diagnostic use in patients with differentiated thyroid cancer (11, 12, 13). In these patients, rhTSH stimulates RAIU in thyroid remnants or thyroid cancer tissue. Recently, we reported that the administration of a single, low dose of rhTSH also considerably increases RAIU in patients with nodular goiter. A dose of 0.01 mg rhTSH given 24 h before ^{131}I administration increased 24-h RAIU from 29 to 51%, on average, and 0.03 mg rhTSH given 24 h before ^{131}I administration increased 24-h RAIU from 33 to 63%, on average (14). These observations suggest that administration of rhTSH before ^{131}I therapy for nodular goiter might allow treatment with lower doses of ^{131}I without diminishing the radiation-absorbed dose in the thyroid.

Nodular goiters are characterized not only by a relatively low uptake of radioiodine but also by an irregular distribution of radioiodine on thyroid scintigrams. The regional distribution of radioiodine in nodular goiters is likely to be dependent on the level of TSH stimulation, with some parts of the goiter needing higher circulating TSH levels to reach sufficient radioiodine uptake than other parts. It is unknown whether giving rhTSH before radioiodine administration preferentially stimulates radioiodine uptake in areas with a relatively high baseline uptake (hot areas) or in those with a relatively low baseline uptake (cold areas) or that radioiodine uptake in hot and cold areas is equally stimulated. If radioiodine uptake in at least some of the cold areas of the goiter would be increased by pretreatment with rhTSH, thyroid volume reduction of nodular goiters by radioiodine therapy might be improved by pretreatment with rhTSH. Therefore, the purpose of this study was to investigate whether pretreatment with rhTSH causes changes in the regional distribution of radioiodine on thyroid scintigrams in patients with nodular goiter.

Patients and Methods

Patients

Twenty-six patients with nodular goiter (23 females and 3 males; age, 62 ± 9 yr, mean ± SD; range, 45–74 yr), who were referred for radioiodine therapy to reduce thyroid volume, participated in the study. All patients had a negative test result (<1 IU/liter) for serum levels of TSH receptor binding antibodies (DYNOtestTRAK human, Brahms Diagnostica GmbH, Hennigsdorf, Germany). The mean thyroid weight, as estimated from planar thyroid scintigraphy (15), was 165 ± 72 g (mean ± SD; range, 60–300 g). All patients had normal serum levels of free T_4 (FT_4; chemiluminescent immunoassay; ACS:180 FrT_4, Chiron Corp., Fernwald, Germany) and total T_3 (chemiluminescent immunoassay; ACS T_3, Ciba Diagnostics Corp., Medfield MA), whereas the serum TSH level (two-site chemiluminometric immunoassay; ACS TSH-3, Ciba Diagnostics Corp.; normal range, 0.2–5.5 mU/liter) was either normal (22 patients) or below normal (4 patients). Based on the results of careful palpation of the thyroid, followed by fine needle aspiration biopsy of dominant nodules and of those that had a different consistency from other nodules within the gland, there was no suspicion of thyroid malignancy in any of the patients. None of the patients had a history of significant cardiopulmonary disease or a recent history of taking any medication known to affect thyroid function or RAIU. Patients had not received iodine-containing agents in the last 6 months. An electrocardiogram, complete blood count, liver enzyme determinations, plasma creatinine and glucose measurements, and screening urinalysis did not show abnormalities in any of the patients. The study was approved by the institutional human research committee, and written informed consent was obtained from all patients.

Baseline planar thyroid scintigraphy and RAIU measurements

For thyroid scintigraphy, all 26 patients received a dose of 1 mCi (40 MBq) sodium (^{123}I) iodide as an oral solution. In 17 patients, administration of ^{123}I was combined with administration of 20 μCi (0.8 MBq) sodium (^{131}I) iodide for measurements of RAIU and effective half-time of radioiodine in the thyroid (results of effective half-time measurements not included in the present report). In the remaining nine patients, RAIU measurements were performed with ^{123}I, and the effective half-time of radioiodine in the thyroid was not measured.

Twenty-four hours after radioiodine administration, the thyroid region was imaged in the anterior plane for a preset time of 10 min with a single-headed gammacamera (Philips Medical Systems, Eindhoven, The Netherlands), using a low-energy general purpose collimator. A 20% energy window around the 159 keV photon peak of ^{123}I and a 256 x 256 matrix were used.

In the patients who had received both ^{123}I and ^{131}I, RAIU was measured as percentage of the administered dose of ^{131}I, corrected for physical decay, at 3, 6, 24, 48, 72, and 168 h, using a 3-inch x 3-inch NaI(Tl) detector. Deadtime corrections were made using standard software. It was checked that the use of the net area under the 364 keV peak of ^{131}I prohibited any interference of the low-energy photons of ^{123}I with RAIU measurements. In the patients who had received ^{123}I only, RAIU was measured as percentage of the administered dose of ^{123}I, corrected for physical decay, at 3, 6, 24, and 48 h using the same 3-inch x 3-inch NaI(Tl) detector. The net area under the 159 keV peak of ^{123}I was used.

Thyroid planar scintigraphy and RAIU measurements after administration of rhTSH

At least 2 wk after the baseline investigation, a second thyroid scintigraphy and RAIU measurement were performed as described before, but this time after pretreatment with rhTSH. Twenty-four hours before radioiodine administration, rhTSH was injected in the quadriceps muscle in a dose of either 0.01 mg (n = 10) or 0.03 mg (n = 16). Before injection, freeze-dried rhTSH (ampoules containing 0.9 mg rhTSH; Thyrogen, Genzyme Transgenics Corp., Cambridge, MA) was reconstituted with 1.2 ml sterile water. Then, part of the obtained solution was diluted with saline to a final concentration of 0.05 mg/ml.

The 17 patients who had received the combination of ^{131}I and ^{123}I in the baseline investigation received again both ^{131}I (20–40 μCi; 0.8–1.6 MBq) and ^{123}I (1 mCi; 40 MBq). Ten of these patients were pretreated with 0.01 mg rhTSH, and 7 with 0.03 mg rhTSH. The nine patients who had received only ^{123}I in the baseline investigation received again only ^{123}I (1 mCi; 40 MBq) and were pretreated with 0.03 mg rhTSH.

Comparison of baseline planar thyroid scintigraphy and planar thyroid scintigraphy after administration of rhTSH

To compare the thyroid scintigram after rhTSH administration (rhTSH scintigram) of each patient with the baseline scintigram, all scintigrams were corrected for background activity using a region immediately below the thyroid as background. Then, rhTSH scintigrams were moved into exactly the same position in the field of view as the baseline scintigrams, using standard software.

In the baseline scintigrams, regions of interest (ROIs) of 1 cm^2 were placed in the region corresponding with the highest number of counts per square centimeter (ROI_{max}). Then, a ROI corresponding with 90% of counts of ROI_{max} was sought, thereafter a ROI corresponding with 80% of counts of ROI_{max}, *etc.*, until ROI_{min}, the region with the lowest number of counts per square centimeter, was reached. The number of counts in each ROI was recorded. The ROIs were saved and then placed in exactly the same position in the rhTSH scintigrams. Again, the numbers

of counts in the ROIs were recorded. For each ROI, the ratio between the number of counts in the rhTSH scintigram and that in the baseline scintigram was calculated. This ratio was corrected for the difference in the total number of counts in the entire thyroid in the rhTSH scintigram and that in the baseline scintigram, resulting in a normalized count ratio in each ROI, according to the following formula:

Normalized count ratio in each ROI

$$= \frac{\text{[counts ROI (rhTSH study) / counts ROI (baseline study)]}}{\text{[counts entire thyroid (rhTSH) / counts entire thyroid (baseline)]}}$$

To compare the uniformity of uptake of radioiodine throughout the whole thyroid gland, for each individual patient the mean and SD of the numbers of counts per pixel in the thyroid scintigram were calculated in the baseline study as well as in the rhTSH study. Thereafter, the coecient of variation [CV = (SD/mean) x 100%] was calculated for each thyroid scintigram.

Statistical analyses

The mean values ± SD are given. Statistical analyses were done using the Mann-Whitney *U* test for unpaired observations (*P* values denoted as *P*) and the Wilcoxon sign-rank test for paired observations (*P* values denoted as *P**). The level of significance was 0.05.

Results

On visual inspection, baseline planar thyroid scintigrams showed the typical scintigraphic appearance of a nodular goiter, *i.e.* heterogeneous uptake of radioiodine with areas of increased and decreased radioiodine uptake, in all patients. In general, the rhTSH scintigrams also showed heterogeneous uptake of radioiodine. In some patients (*e.g.* no. 15 and 20; Fig. 1), the distribution of radioiodine in the rhTSH scintigram was considerably more homogeneous than in the baseline scintigram. Interestingly, in a few patients (*e.g.* no. 11 and 15; Fig. 1) originally cold areas had changed into hot ones, whereas originally hot areas had changed into cold ones.

Figure 2 shows the normalized count ratios in the ROIs of all 26 patients. A normalized count ratio of more than 1.00 in a ROI indicates an increase of radioiodine uptake in this ROI relative to the uptake in the entire thyroid gland, and a normalized count ratio of less than 1.00 indicates a decrease of radioiodine uptake in the ROI relative to the uptake in the entire thyroid gland. In most patients, pretreatment with rhTSH caused a relatively larger increase in radioiodine uptake in cold areas, compared with the increase in radioiodine uptake in the entire thyroid. Furthermore, in most patients rhTSH pretreatment led to a relatively smaller increase in radioiodine uptake in hot areas, compared with the increase in radioiodine uptake in the entire thyroid.

Table 1 shows that the ratio between 24-h RAIU after rhTSH administration and the baseline 24-h RAIU (RAIU ratio) was 2.12 ± 0.53 (range, 1.23–3.11). Table 1 also shows that the normalized count ratio in the ROI with the lowest number of counts in the baseline study (normalized count ratio ROI_{min}) was 1.30 ± 0.29 (range, 0.93–2.04), which is significantly different from 1.00 ($P^* < 0.0001$). The normalized count ratio in the ROI with the highest number of counts in the baseline study (normalized count ratio ROI_{max}) was 0.87 ± 0.16 (range, 0.50–1.11), which is also significantly different from 1.00 ($P^* < 0.0005$). The normalized count ratio in ROI_{min} was more than 1.00 in 81%, more than 1.10 in 69%, and more than 1.20 in 58% of the 26 patients, respectively. The normalized count ratio in ROI_{max} was lower than 1.00 in 77%, lower than 0.90 in 54%, and lower than 0.80 in 27% of the 26 patients, respectively. The combination of a normalized count ratio in ROI_{min} of more than 1.00 and a normalized count ratio in ROI_{max} of less than 1.00 was found in 73% of patients. Using cut-off levels of 1.10/0.90 and 1.20/0.80, respectively, this percentage was 50 and 23%. There were no significant differences in normalized count ratios in ROI_{min} or ROI_{max} among the patients who had received 0.01 mg rhTSH and the combination of ^{123}I and ^{131}I, those who had received 0.03 mg rhTSH and the combination of ^{123}I and ^{131}I, and those who had received 0.03 mg rhTSH and only ^{123}I ($P > 0.1$ for all comparisons).

Patients with a serum TSH level of 0.5 mU/liter or lower in the baseline study had a significantly higher normalized count ratio in ROI_{min} than patients with a serum TSH level higher than 0.5 mU/liter [1.40 ± 0.31 (n = 16) *vs.* 1.14 ± 0.16 (n = 10); $P < 0.02$]. All five patients with a normalized count ratio in ROI_{min} of 1.5 or more had a baseline serum TSH level of 0.5 mU/liter or less. The normalized count ratio in ROI_{max} did not differ significantly between patients with a baseline serum TSH level of 0.5 mU/liter or lower (0.85 ± 0.19) and those with a baseline serum TSH level higher than 0.5 mU/liter (0.91 ± 0.09).

The coefficient of variation of the numbers of counts per pixel in the thyroid scintigram was 60 ± 11% in the baseline study and 55 ± 11% in the rhTSH study ($P < 0.001$), indicating a significantly more homogeneous uptake of radioiodine throughout the thyroid gland after rhTSH administration.

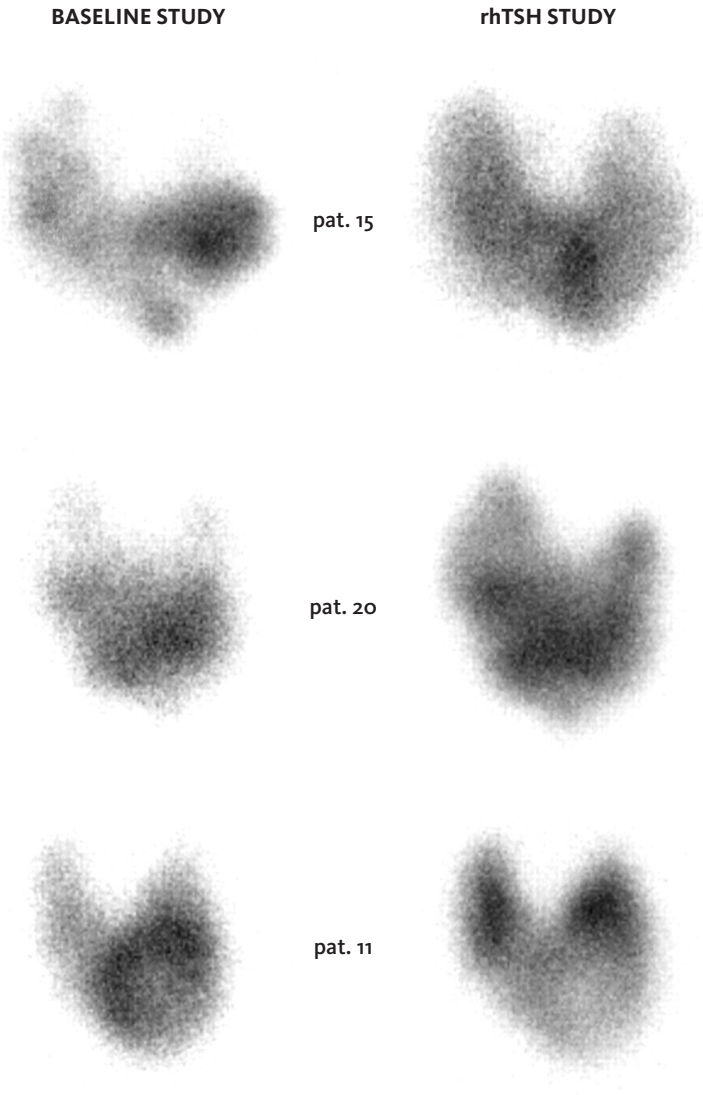


Figure 1. *Examples of planar anterior scintigrams of the thyroid in the baseline study (left panels) and in the rhTSH study (right panels). In patients 15 (upper panels) and 20 (middle panels), the distribution of radioiodine in the rhTSH scintigram is much more homogeneous than in the baseline scintigram. In patient 15, the rhTSH study shows, in comparison with the baseline study, not only an increased uptake in relatively cold areas but also a decreased uptake in the hot area in the left lobe. In patient 11 (lower panels), the rhTSH study shows, in comparison with the baseline study, an increased uptake in both upper poles, whereas the left lower pole shows a decreased uptake.*

Table 1. *Serum TSH level at the time of the baseline study, peak serum TSH, FT_4 and T_3 levels reached in the rhTSH study, 24-h RAIU in the baseline study, 24-h RAIU in the rhTSH study, ratio between 24-h RAIU in the rhTSH study and 24-h RAIU in the baseline study (RAIU ratio), normalized count ratio in the ROI with the lowest number of counts in the baseline study (normalized count ratio ROI$_{min}$), normalized count ratio in the ROI with the highest number of counts in the baseline study (normalized count ratio ROI$_{max}$) in the 26 patients*

Patient no.	Serum TSH baseline study (mU/liter)	Peak TSH rhTSH study (mU/liter)[a]	Peak FT4 rhTSH study (pmol/liter)[a]	Peak T3 rhTSH study (nmol/liter)[a]	24-h RAIU baseline study (%)	24-h RAIU rhTSH study (%)	RAIU ratio[b]	Normalized count ratio ROI-min	Normalized count ratio ROI-max	Coefficient of variation baseline study (%)	Coefficient of variation rhTSH study (%)
1	0.17	4.20	15.1	2.3	19	38	2.00	1.80	0.60	67	51
2	0.45	3.60	14.7	3.1	27	39	1.44	1.30	0.96	62	59
3	0.47	5.00	18.7	3.0	17	36	2.12	1.52	0.96	71	69
4	0.50	5.30	12.2	2.2	23	50	2.17	1.54	1.11	81	86
5	0.80	4.00	17.1	2.7	16	28	1.75	1.20	0.87	47	40
6	1.10	5.40	23.8	2.4	22	37	1.68	1.41	0.90	55	50
7	0.70	5.60	16.5	2.1	21	61	2.90	0.93	1.02	50	45
8	1.50	5.90	19.1	3.0	30	45	1.50	1.05	0.95	49	53
9	0.03	3.30	23.6	3.5	32	60	1.88	1.42	0.61	56	43
10	0.25	4.10	16.6	2.8	47	58	1.23	0.98	0.96	49	46
Mean ± SD	0.60 ± 0.45	4.64 ± 0.91	17.7 ± 3.7	2.7 ± 0.5	25 ± 9	45 ± 12	1.87 ± 0.47	1.32 ± 0.28	0.89 ± 0.17	59 ± 11	54 ± 14
11	0.42	17.50	19.5	3.3	25	62	2.48	2.04	0.84	48	44
12	0.90	14.90	18.7	2.2	43	75	1.74	1.12	0.72	43	44
13	0.49	20.00	26.6	3.5	25	59	2.36	1.22	0.87	54	51
14	0.27	14.10	21.0	3.2	48	65	1.35	1.08	0.89	51	50
15	0.03	13.60	23.6	3.8	32	66	2.06	1.43	0.50	56	45
16	0.48	16.00	23.0	3.7	22	58	2.64	1.48	1.04	52	47
17	2.30	14.20	19.2	2.4	30	44	1.47	1.08	0.96	52	48
Mean ± SD	0.70 ± 0.75	15.76 ± 2.30	21.66 ± 2.88	3.2 ± 0.6	32 ± 10	61 ± 9	2.01 ± 0.51	1.35 ± 0.35	0.83 ± 0.18	51 ± 4	47 ± 3
18	1.00	13.90	19.5	3.3	21	47	2.24	1.17	0.89	70	65
19	0.34	7.70	25.7	3.2	22	49	2.23	0.96	1.05	63	62
20	0.41	12.10	24.1	2.3	17	52	3.06	1.71	0.67	76	58
21	2.70	8.30	15.7	2.5	21	40	1.90	1.15	0.93	68	59
22	0.03	14.90	32.8	5.4	27	68	2.52	1.49	0.77	53	44
23	1.20	10.50	18.7	3.0	27	53	1.96	0.95	1.01	70	68
24	0.31	9.60	14.8	2.2	17	46	2.71	1.48	0.68	79	63
25	0.22	14.30	21.6	3.3	26	69	2.65	0.96	1.02	61	55
26	1.10	10.20	16.9	2.9	19	59	3.11	1.37	0.83	74	76
Mean ± SD	0.81 ± 0.82	11.28 ± 2.65	21.1 ± 5.7	3.1 ± 1.0	22 ± 4	54 ± 10	2.49 ± 0.44	1.25 ± 0.28	0.87 ± 0.14	68 ± 8	61 ± 9
Mean ± SD	0.70 ± 0.66	9.93 ± 5.02	20.0 ± 4.5	3.0 ± 0.7	26 ± 9	53 ± 12	2.12 ± 0.53	1.30 ± 0.29	0.87 ± 0.16	60 ± 11	55 ± 11
Range	0.03–2.70	3.30–20.00	12.2–32.8	2.1–5.4	16–48	28–75	1.23–3.11	0.93–2.04	0.50–1.11	43–81	40–86

Patients 1-10 received 0.01 mg rhTSH and tracer doses of both ^{123}I and ^{131}I. Patients 11-17 received 0.03 mg rhTSH and tracer doses of both ^{123}I and ^{131}I. Patients 18-26 received 0.03 mg rhTSH and a tracer dose of ^{123}I only.

[a] Serum TSH, FT_4, and T_3 measurements were performed 2, 5, 8, 24, 48, 72, and 96 h after rhTSH administration. Peak levels of TSH were reached at 5 or 8 h after rhTSH administration in all patients. Peak levels of FT_4 and T_3 were reached between 5 and 96 h after rhTSH administration.

[b] RAIU ratio in patients who received 0.03 mg rhTSH (no. 11-26) significantly higher ($P < 0.05$) than RAIU ratio in patients who received 0.01 mg rhTSH (no. 1-10).

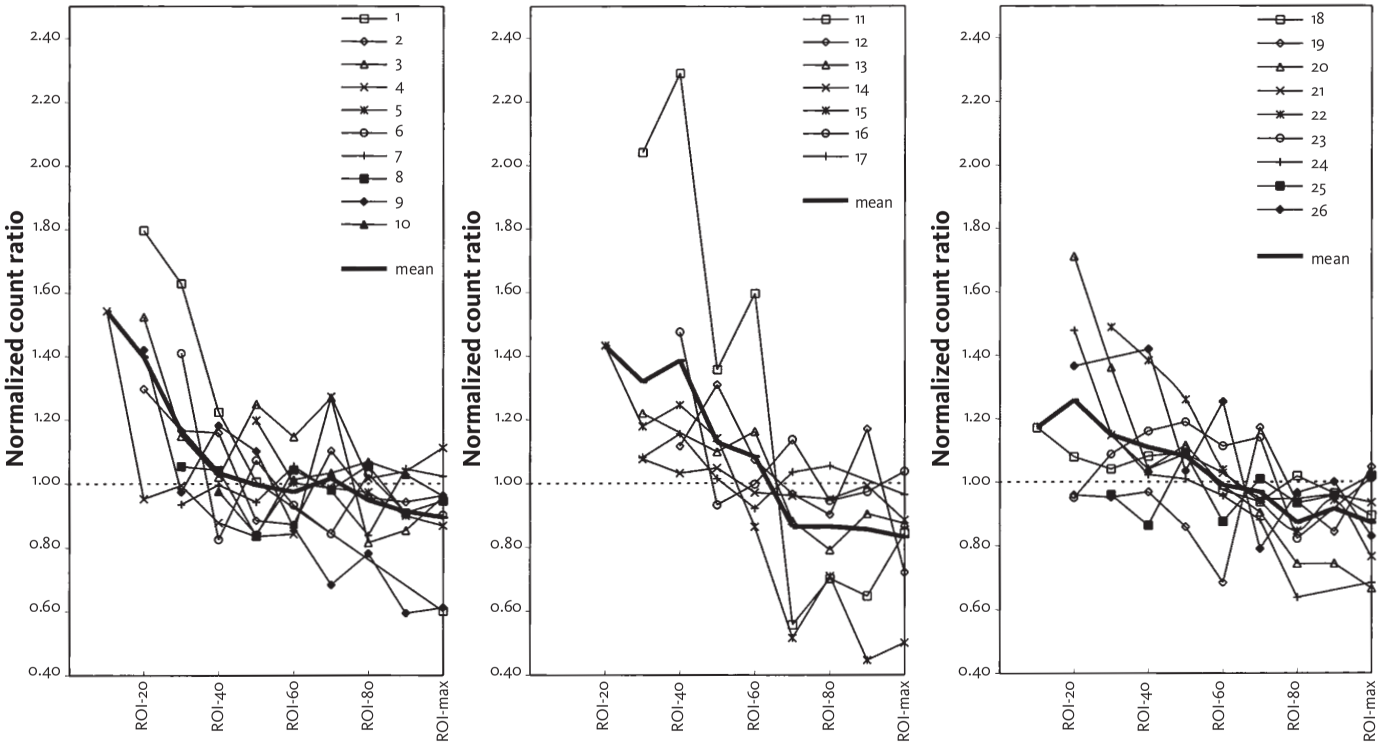


Figure 2. *Normalized count ratios of ^{123}I uptake in each ROI of the 26 patients. Normalized count ratios are calculated as described in the text (see Patients and Methods). On the x-axis, ROI$_{max}$ indicates the ROI with the highest number of counts per square centimeter in the baseline study, ROI-80 indicates a ROI in the baseline study in which the number of counts is 80% of that in ROI$_{max}$, etc. Ten patients (no. 1–10) received 0.01 mg rhTSH and tracer doses of both ^{123}I and ^{131}I (left). Seven patients (no. 11–17) received 0.03 mg rhTSH and tracer doses of both ^{123}I and ^{131}I (middle). Nine patients (no. 18–26) received 0.03 mg rhTSH and a tracer dose of ^{123}I only (right).*

Discussion

The present study demonstrates that administration of a single, low dose of rhTSH before a diagnostic dose of radioiodine not only doubles 24-h thyroid RAIU but also induces significant changes in the regional distribution of radioiodine on thyroid scintigrams in patients with nodular goiter. In most patients, pretreatment with rhTSH caused a larger increase in radioiodine uptake in relatively cold areas and a smaller increase in radioiodine uptake in relatively hot areas, compared with the increase in radioiodine uptake in the entire thyroid. As a result, the distribution of radioiodine on the rhTSH scintigram was significantly more homogeneous than that on the baseline scintigram, as demonstrated by a significantly lower mean coefficient of variation of the numbers of counts per pixel in the thyroid scintigram after rhTSH administration. In patients with a baseline serum TSH level of 0.5 mU/liter or lower, the increase in radioiodine uptake in relatively cold areas was significantly larger than in patients with a baseline serum TSH level higher than 0.5 mU/liter. This suggests that especially in patients with a low baseline serum TSH level, a more homogeneous distribution of radioiodine on the thyroid scintigram can be reached by pretreatment with rhTSH.

Our observations have important consequences when rhTSH pretreatment is considered as an adjunct to radioiodine therapy for volume reduction of nodular goiters. From our study, one may derive that the effects of rhTSH pretreatment for this purpose will depend on the decision whether or not the therapeutic dose of radioiodine is lowered according to the rhTSH-induced increase in 24-h RAIU. When the therapeutic dose of radioiodine is lowered according to the rhTSH-induced increase in 24-h RAIU, in a number of areas with relatively low baseline radioiodine uptake the 24-h retained amount of radioiodine per gram of thyroid tissue will nevertheless increase, which might improve the efficacy of radioiodine therapy for volume reduction of the goiter. In contrast, in a number of areas with relatively high baseline radioiodine uptake, the 24-h retained amount of radioiodine per gram of thyroid tissue will decrease. However, it is not likely that this will negatively influence the efficacy of radioiodine therapy; without rhTSH pretreatment, the 24-h retained amount of radioiodine per gram in these hot areas would have been considerably higher than the average retained amount per gram in the entire thyroid, and with rhTSH pretreatment, in most of these areas at least the average amount of radioiodine per gram in the entire thyroid will be retained at 24 h.

When the therapeutic dose of radioiodine is not lowered according to the rhTSH-induced increase in 24-h RAIU, but based on the baseline 24-h RAIU, most areas in the goiter, cold as well as hot ones, will retain a higher amount of radioiodine per gram of thyroid tissue with pretreatment with rhTSH than without pretreatment with rhTSH. This conclusion can be drawn from multiplying the normalized

count ratio with the RAIU ratio (see Table 1). This multiplication indicates the difference in uptake in a ROI between the rhTSH study and the baseline study when the dose of radioiodine in both studies is the same. From the calculation "normalized count ratio x RAIU ratio" in ROI_{min} and ROI_{max} in the individual patients, one may derive that 24-h radioiodine uptake in the area with the lowest baseline radioiodine uptake (ROI_{min}) will increase by a factor of three (normalized count ratio ROI_{min} x RAIU ratio, 2.81 ± 1.08, mean ± SD; range, 1.21–5.23) and that 24-h radioiodine uptake in the area with the highest baseline radioiodine uptake (ROI_{max}) will increase 2-fold (normalized count ratio ROI_{max} x RAIU ratio, 1.84 ± 0.55, mean ± SD; range, 1.03–2.96). Not lowering the therapeutic dose of radioiodine according to the rhTSH-induced increase in 24-h RAIU may be advantageous for the efficacy of the therapy. However, this dosage regimen carries a higher risk of inducing radiation thyroiditis.

It should be noted that in a significant number of patients, rhTSH-induced increases in radioiodine uptake in areas with a relatively low baseline radioiodine uptake were small or even absent. This is not surprising, because part of these cold areas represent mainly cystic or fibrotic tissue or thyroid follicular cells that have (partially) lost their ability to express the Na^+/I^- symporter protein (16, 17). Such parts of the goiter cannot take up radioiodine, not even after heavy TSH stimulation. Furthermore, a relative increase in radioiodine uptake in cold areas on a planar scintigram should be cautiously interpreted because planar scintigraphy is a two-dimensional method. It cannot be excluded that an increase in radioiodine uptake in a relatively cold area by pretreatment with rhTSH is caused by an increase in radioiodine uptake in thyroid tissue lying anteriorly or posteriorly of a cold area that itself does not increase in uptake. In a small number of the patients described in the present study, single photon emission computed tomography (SPECT), a three-dimensional imaging method, was performed (our unpublished observations). Transaxial SPECT slices showed that in some cold areas rhTSH administration increased radioiodine uptake only in a rim of thyroid tissue, whereas the central part of the area showed no change in uptake. However, in other cold areas, SPECT images showed an increase in radioiodine uptake in the entire area, from anterior to posterior.

Seventeen of the 26 patients in our study received the combination of ^{123}I and ^{131}I. The high energy photons of ^{131}I will have caused some scatter in the ^{123}I thyroid scintigrams. However, the dose of ^{131}I was only a small fraction of the dose of ^{123}I, and the regional distribution of ^{131}I within the thyroid is the same as that of ^{123}I. Therefore, the effect of scatter of ^{131}I on normalized count ratios will have been negligible. This was confirmed by the results in the patients who received only ^{123}I, which were not different from those in the patients who received both ^{123}I and ^{131}I.

Our results do not allow the conclusion that 0.01 mg is the minimally effective dose of rhTSH in stimulating 24-h RAIU. However, the peak serum TSH level reached after administration of 0.01 mg rhTSH was only 4.64 mU/liter, on average. It is not likely that administration of a lower dose of rhTSH, resulting in peak serum TSH levels significantly lower than 4 mU/liter, will effectively elevate 24-h RAIU in these patients. Our data also do not demonstrate that the 0.03 mg dose is the maximally effective dose of rhTSH in stimulating 24-h RAIU. In fact, it is likely that a higher dose will increase 24-h RAIU even more. However, even when a higher dose of rhTSH is more effective in stimulating 24-h RAIU, it is doubtful whether this is clinically relevant, because with the 0.01 and 0.03 mg doses already a doubling of 24-h RAIU can be reached. Furthermore, larger amounts of thyroid hormones may be released after administration of higher doses of rhTSH.

In conclusion, a single, low dose of rhTSH not only doubled 24-h RAIU in patients with nodular goiter but also caused a more homogeneous distribution of radioiodine within the thyroid gland in the majority of these patients by stimulating radioiodine uptake in relatively cold areas more than in relatively hot areas. This was most marked in patients with a low baseline serum TSH level. Our data suggest that pretreatment with rhTSH might allow treatment with lower doses of ^{131}I. Furthermore, they suggest that despite lowering of the dose of ^{131}I, pretreatment with rhTSH might improve the efficacy of radioiodine treatment for volume reduction of nodular goiters, especially in patients with a low baseline serum TSH level. However, randomized studies comparing the efficacy of radioiodine therapy with and without rhTSH pretreatment have to be awaited before its use can be advised.

Acknowledgments

We thank Bernie Gitmans and Chris Jansen for their help in performing this study.

References

1 **Hegedüs L, Hansen BM, Knudsen N, Hansen JM** 1988 Reduction of size of thyroid with radioactive iodine in multinodular non-toxic goitre. BMJ 297:661–662

2 **Nygaard B, Hegedüs L, Gervil M, Hjalgrim H, Soe-Jensen P, Hansen JM** 1993 Radioiodine treatment of multinodular non-toxic goitre. BMJ 307:828–832

3 **Huysmans DA, Hermus AR, Corstens FH, Barentsz JO, Kloppenborg PW** 1994 Large, compressive goiters treated with radioiodine. Ann Intern Med 121:757–762

4 **Wesche MF, Tiel-van Buul MM, Smits NJ, Wiersinga WM** 1995 Reduction in goiter size by ^{131}I therapy in patients with non-toxic multinodular goiter. Eur J Endocrinol 132:86–87

5 **de Klerk JM, van Isselt JW, van Dijk A, Hakman ME, Pameijer FA, Koppeschaar HP, Zelissen PM, van Schaik JP, van Rijk PP** 1997 Iodine-^{131} therapy in sporadic nontoxic goiter. J Nucl Med 38:372–376

6 **Bonnema SJ, Bertelsen H, Mortensen J, Andersen PB, Knudsen DU, Bastholt L, Hegedüs L** 1999 The feasibility of high dose I^{131} treatment as an alternative to surgery in patients with a very large goiter: effect on thyroid function and size and pulmonary function. J Clin Endocrinol Metab 84:3636–3641

7 **Huysmans D, Hermus A, Edelbroek M, Barentz J, Corstens F, Kloppenborg P** 1997 Radioiodine for nontoxic multinodular goiter. Thyroid 7:235–239

8 **Hermus AR, Huysmans DA** 1998 Treatment of benign nodular thyroid disease. N Engl J Med 338:1438–1447

9 **Nygaard B, Soes-Petersen U, Hoilund-Carlsen PF, Veje A, Holst PE, Vestergaard A, Solling K** 1996 Improvement of upper airway obstruction after ^{131}I-treatment of multinodular nontoxic goiter evaluated by flow volume loop curves. J Endocrinol Invest 19:71–75

10 **Huysmans DA, Buijs WC, van de Ven MT, van den Broek WJ, Kloppenborg PW, Hermus AR, Corstens FH** 1996 Dosimetry and risk estimates of radioiodine therapy for large, multinodular goiters. J Nucl Med 37:2072–2079

11 **Meier CA, Braverman LE, Ebner SA, Veronikis I, Daniels GH, Ross DS, Deraska DJ, Davies TF, Valentine M, DeGroot LJ, Curran P, McEllink K, Reynolds J, Robbins J, Weintraub BD** 1994 Diagnostic use of recombinant human thyrotropin in patients with thyroid carcinoma (phase I/II study). J Clin Endocrinol Metab 78:188–196

12 **Ladenson PW, Braverman LE, Mazzaferri EL, Brucker-Davis F, Cooper DS, Garber JR, Wondisford FE, Davies TF, DeGroot LJ, Daniels GH, Ross DS, Weintraub BD** 1997 Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N Engl J Med 337:888–896

13 **Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, Cooper DS, Graham KE, Braverman LE, Skarulis MC, Davies TF, DeGroot LJ, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Becker DV, Maxon HR 3rd, Cavalieri RR, Spencer CA, McEllin K, Weintraub BD, Ridgway EC** 1999 A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J Clin Endocrinol Metab 84:3877–3885

14 **Huysmans DA, Nieuwlaat WA, Erdtsieck RJ, Schellekens AP, Bus JW, Bravenboer B, Hermus AR** 2000 Administration of a single low dose of recombinant human thyrotropin significantly enhances thyroid radioiodide uptake in nontoxic nodular goiter. J Clin Endocrinol Metab 85:3592–3596

15 **Doering P, Kramer K** 1958 Die Bestimmung des Schilddrüsengewichtes mit der Szintigraphie nach Gabe von Radiojod: Ein Beitrag zur Dosierung des Radioisotopes. Strahlenther 105:245–259

16 **Caillou B, Troalen F, Baudin E, Talbot M, Filetti S, Schlumberger M, Bidart JM** 1998 Na^+/I^- symporter distribution in human thyroid tissues: an immunohistochemical study. J Clin Endocrinol Metab 83:4102–4106

17 **Joba W, Spitzweg C, Schriever K, Heufelder AE** 1999 Analysis of human sodium/iodide symporter, thyroid transcription factor-1, and paired-box-protein-8 gene expression in benign thyroid diseases. Thyroid 9:455–466

chapter

4

4.1

Pretreatment with a Single, Low Dose of Recombinant Human Thyrotropin Allows Dose Reduction of Radioiodine Therapy in Patients with Nodular Goiter

Willy-Anne Nieuwlaat, Dyde A. Huysmans, Harrie C. van den Bosch, C. G. (Fred) Sweep, H. Alec Ross, Frans H. Corstens, and Ad R. Hermus

Departments of Nuclear Medicine (W.-A.N., D.A.H.) and Radiology (H.C.v.d.B.), Catharina Hospital, Eindhoven;
Departments of Endocrinology (W.-A.N., A.R.H.), Chemical Endocrinology (C.G.S., H.A.R.), and Nuclear Medicine (F.H.C.), Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

The Journal of Clinical Endocrinology & Metabolism 2003; 88(7): 3121-3129

4.1

Abstract

In patients with nodular goiter, radioiodine (^{131}I) therapy results in a mean reduction in thyroid volume (TV) of approximately 40% after 1 yr. We have demonstrated that pretreatment with a single, low dose of recombinant human TSH (rhTSH) doubles 24-h radioactive iodine uptake (RAIU) in these patients. We have now studied the safety and efficacy of therapy with a reduced dose of ^{131}I after pretreatment with rhTSH.

Twenty-two patients with nodular goiter received ^{131}I therapy, 24 h after im administration of 0.01 (n = 12) or 0.03 (n = 10) mg rhTSH. In preceding diagnostic studies using tracer doses of ^{131}I, 24-h RAIU without and with rhTSH pretreatment (either 0.01 or 0.03 mg) were compared. Therapeutic doses of ^{131}I were adjusted to the rhTSH-induced increases in 24-h RAIU and were aimed at 100 μCi/g thyroid tissue retained at 24 h. Pretreatment with rhTSH allowed dose reduction of ^{131}I therapy by a factor of 1.9 ± 0.5 in the 0.01-mg and by a factor of 2.4 ± 0.4 in the 0.03-mg rhTSH group ($P < 0.05$, 0.01 *vs.* 0.03 mg rhTSH). Before and 1 yr after therapy, TV and the smallest cross-sectional area of the tracheal lumen were measured with magnetic resonance imaging. During the year of follow-up, serum TSH, free T_4 (FT_4), T_3, and TSH receptor antibodies were measured at regular intervals.

TV before therapy was 143 ± 54 ml in the 0.01-mg group and 103 ± 44 ml in the 0.03-mg rhTSH group. One year after treatment, TV reduction was 35 ± 14% (0.01 mg rhTSH) and 41 ± 12% (0.03 mg rhTSH). In both groups, smallest cross-sectional area of the tracheal lumen increased significantly. In the 0.01-mg rhTSH group, serum FT_4 rose, after ^{131}I treatment, from 15.8 ± 2.8 to 23.2 ± 4.4 pM. In the 0.03-mg rhTSH group, serum FT_4 rose from 15.5 ± 2.5 to 23.5 ± 5.1 pM. Individual peak FT_4 levels, reached between 1 and 28 d after ^{131}I treatment, were above the normal range in 12 patients. TSH receptor antibodies were negative in all patients before therapy and became positive in 4 patients. Hyperthyroidism developed in 3 of these 4 patients between 23 and 25 wk after therapy.

In conclusion, in patients with nodular goiter pretreatment with a single, low dose of rhTSH allowed approximately 50–60% reduction of the therapeutic dose of radioiodine without compromising the efficacy of TV reduction.

Introduction

Radioiodine (^{131}I) is an effective therapy for thyroid volume (TV) reduction in patients with nontoxic, nodular goiter. In a number of studies, it has been reported that ^{131}I treatment leads to a decrease in goiter size of approximately 40% after 1 yr (1, 2, 3, 4, 5, 6, 7) and of 50–60% after 3–5 yr (2, 8, 9). In most patients, compressive symptoms improved as well (3). The reduction of compressive symptoms was accompanied by significant tracheal widening and improvement in respiratory function (3, 10).

In the reported studies, a single dose of approximately 100 μCi (3.7 MBq) of ^{131}I per gram of thyroid tissue, corrected for radioactive iodine uptake (RAIU) at 24 h, was given. In patients with nontoxic, nodular goiter, RAIU is usually rather low. As a result, high doses of ^{131}I are often needed, causing a relatively high radiation burden to extrathyroidal tissues (11). One of the causes of a low RAIU in these patients is a low-normal or below-normal serum level of TSH.

Recently, we reported that, in patients with nodular goiter, administration of a single, low dose of 0.01 or 0.03 mg recombinant human TSH (rhTSH) doubled 24-h RAIU (12). We also described that pretreatment with rhTSH caused a more homogeneous distribution of radioiodine on the thyroid scintigrams of nodular goiters (13). These observations suggest that administration of rhTSH before ^{131}I therapy for volume reduction of nontoxic, nodular goiter may allow treatment with lower doses of ^{131}I in these patients without diminishing the radiation-absorbed dose in the thyroid.

Before rhTSH can be advised as an adjunct to ^{131}I therapy in patients with nontoxic, nodular goiter, the safety of the administration of a therapeutic dose of ^{131}I after pretreatment with rhTSH has to be investigated. First, it has to be ascertained that pretreatment with rhTSH does not exacerbate the increases in serum thyroid hormone levels commonly seen in the first weeks after ^{131}I treatment of nontoxic, nodular goiter. Second, it has to be determined that this therapy does not cause acute enlargement of the goiter, compressing the trachea further (14). Therefore, the first aim of this study was to determine the short-term safety of the administration of a therapeutic dose of ^{131}I after pretreatment with a single, low dose (0.01 or 0.03 mg) of rhTSH. In this study, the therapeutic dose of ^{131}I was adjusted to the rhTSH-induced increase in 24-h RAIU, as determined in a diagnostic study using a tracer dose of ^{131}I. The second aim was to determine the efficacy of this therapy in terms of TV reduction and increase of the smallest cross-sectional area of the tracheal lumen (SCAT) after 1 yr.

Patients and Methods

Patients

Twenty-two patients with nodular goiter (18 females and 4 males; 60 ± 9 yr old; mean ± SD; range, 45–73 yr), who were referred for ^{131}I therapy to reduce TV, participated in this study. All patients had a negative test result (<1 IU/liter) for serum levels of TSH receptor antibodies (TRAbs) (DYNOtest TRAK human; Brahms Diagnostica GmbH, Hennigsdorf, Germany). All patients had normal serum levels of free T_4 (FT_4) (chemiluminescent immunoassay, ACS:180 FrT_4; Chiron Corp., Fernwald, Germany; normal values, 9.0–22.3 pM) and total T_3 (chemiluminescent immunoassay, ACS T3; Ciba Diagnostics Corp., Medfield, MA; normal values, 1.0–3.0 nM), whereas the serum TSH level (2-site chemiluminometric immunoassay, ACS TSH-3; Ciba Diagnostics Corp.; normal values, 0.2–5.5 mU/liter) was normal (19 patients) or below normal (3 patients). Based on the results of careful palpation of the thyroid, followed by fine-needle aspiration biopsy of dominant nodules and of those that had a different consistency from other nodules within the gland, there was no suspicion of thyroid malignancy in any of the patients. None of the patients had a recent history of taking any medication known to affect thyroid function or RAIU. Patients had not received iodine-containing agents in the last 6 months. Twenty-four-hour iodide excretion was 169 ± 71 μg (range, 80–330 μg). An electrocardiogram, complete blood count, liver enzyme determinations, plasma creatinine and glucose measurements, and screening urinalysis did not show abnormalities in any of the patients. The institutional human research committee approved the study, and written informed consent was obtained from all patients.

Diagnostic investigations

A diagnostic dose of 20 μCi (0.8 MBq) sodium (^{131}I) iodide was administered as an oral solution, together with 1 mCi (40 MBq) sodium (^{123}I) iodide for thyroid scintigraphy. RAIU as a percentage of the administered dose of ^{131}I, corrected for physical decay, was measured at 24 h using a 3 x 3-in. NaI(Tl) detector. Deadtime corrections were made using standard software. The use of the net area under the 364-kiloelectron volts peak of ^{131}I was checked to prohibit any interference of the low-energy photons of ^{123}I with RAIU measurements. Thyroid scintigraphy in the 159-kiloelectron volts window of ^{123}I was performed 24 h after radioiodide administration. All thyroid scintigrams showed a heterogeneous uptake.

The influence of rhTSH on RAIU was investigated in each patient at least 2 wk after radioiodine administration for the baseline RAIU. After reconstitution of freeze-dried rhTSH (ampoules containing 0.9 mg rhTSH, Thyrogen; Genzyme Transgenics Corp., Cambridge, MA) with 1.2 ml sterile water, part of the obtained solution was diluted with saline to a final concentration of 0.05

mg/ml. Immediately after dilution, 0.01 mg (0.2 ml; n = 12) or 0.03 mg (0.6 ml; n = 10) rhTSH was injected in the quadriceps muscle. A diagnostic dose of 20–40 μCi (0.8–1.6 MBq) sodium ^{131}I was administered as an oral solution [together with 1 mCi (40 MBq) sodium ^{123}I for thyroid scintigraphy] 24 h after the administration of rhTSH. RAIU as a percentage of the administered dose of ^{131}I, corrected for background activity from the radioiodine from the baseline investigation and for physical decay, was measured at 24 h. Thyroid scintigraphy was performed 24 h after radioiodine administration (results not included in the present report).

Radioiodine therapy

Thirty-five ± 21 d (range, 13–84 d) after the diagnostic rhTSH study, patients received a second injection of rhTSH in the quadriceps muscle, using the same rhTSH dose as was given for the diagnostic study. Twenty-four hours later, radioiodine was given as a single oral dose on an inpatient basis. The therapeutic dose of ^{131}I was adjusted to the rhTSH-induced increase in 24-h RAIU, as determined for each individual patient in the preceding diagnostic study, and was aimed at delivering 100 μCi (3.7 MBq) ^{131}I/g of thyroid tissue retained at 24 h, according to the following formula: administered activity (GBq) = [thyroid weight (g) x 0.37]/24-h thyroid RAIU (%) (15). For calculation of the therapeutic dose of radioiodine, we estimated thyroid weight from the planimetric surface on the baseline scintigram, using the formula of Doering and Kramer (16): thyroid weight (g) = 0.326 x (surface in cm^2)$^{3/2}$. Mean thyroid weight, as estimated from the planar thyroid scintigraphies, was 148 ± 62 g (range, 70–265 g).

Follow-up investigations

Symptoms and signs of thyrotoxicosis, thyroiditis, or tracheal compression and vital signs (blood pressure, pulse rate, and body temperature) were recorded immediately before and 2, 5, and 8 h after rhTSH pretreatment, as well as immediately before and 1, 2, 3, 7, 10, 14, 21, 28, 56, and 84 d after ^{131}I therapy.

Before and 1 wk and 1 yr after radioiodine treatment, TV and the SCAT were measured. TV was measured by magnetic resonance imaging (MRI) (MRI Intera software release 8.1.3; Philips Medical Systems, Best, The Netherlands) operating at a field strength of 1.5 tesla. Transversal, sagittal, and coronal T_1-weighted images [TR (repetition time) = 600 ms; echo time = 14 ms] were obtained by using a standard quadrature neck coil. The slices had a thickness of 4 mm (with an interslice gap of 0.4 mm) in the transversal plane and 3 mm (with an interslice gap of 0.3 mm) in the coronal and sagittal planes and covered the entire thyroid gland. The thyroid outline was drawn manually on each slice, and the surface of the traced areas was calculated (Easy Vision software; Philips Medical Systems). To calculate the TV, we multiplied the sum of the traced sur-

faces in each plane by the sum of the slice thickness and interslice gap. TV, as used hereafter, is the mean of the measurements in the three imaging planes. The precision of TV measurement by MRI is high. The intraobserver coefficient of variation is 2.2% ± 2.0%, and the interobserver coefficient of variation is 4.1% ± 2.2% (17). SCAT, a measure of tracheal compression (18), was determined by manually drawing a line along the outer contour of the trachea in the transversal T_1-weighted images. All measurements were done blinded.

Serum TSH, FT_4, and T_3 levels were measured immediately before rhTSH pretreatment and 2, 5, and 8 h after rhTSH administration, as well as immediately before and 1, 2, 3, 7, 10, 14, 21, 28, and 56 d and 3, 6, 9, and 12 months after ^{131}I treatment. Serum levels of C-reactive protein (CRP) (BNII hs-CRP; Dade Behring, Deerfield, IL; normal value < 12.5 mg/liter) was measured immediately before and 7, 10, 14, 21, 28, 42, and 56 d and 3 months after ^{131}I treatment. Serum levels of TRAbs (DYNOtest TRAK human; Brahms Diagnostica GmbH; negative value < 1 IU/liter and positive value > 1.5 IU/liter) and of anti-TPO antibodies (DYNOtest anti-TPOn; Brahms Diagnostica GmbH; negative value < 60 U/ml) were measured before and 3, 6, 9, and 12 months after ^{131}I therapy.

Statistical analyses

The mean ± SD values are given. Statistical analyses were done using the Mann-Whitney *U* test for unpaired observations (*P* values denoted as *P*), the Wilcoxon sign-rank test for paired observations (*P* values denoted as *P**), and Spearman's test for nonparametric correlations (*P* values denoted as *P***). The level of significance was 0.05.

Results

Diagnostic investigations

Effect of rhTSH administration on RAIU (Table 1). In the diagnostic studies, using a tracer dose of ^{131}I, administration of 0.01 mg rhTSH, 24 h before ^{131}I, increased 24-h RAIU from 27 ± 8% to 50 ± 11% (*P** < 0.005). Administration of 0.03 mg rhTSH, 24 h before ^{131}I, increased 24-h RAIU from 22 ± 4% to 54 ± 9% (*P** < 0.01). The ratio between 24-h RAIU after rhTSH and baseline 24-h RAIU (RAIU ratio) was significantly higher (*P* < 0.05) in patients who received 0.03 mg rhTSH (2.4 ± 0.4) than in those who received 0.01 mg rhTSH (1.9 ± 0.5).

Calculation of dose reduction of radioiodine therapy (Table 1, Fig. 1). In each patient, the therapeutic dose of ^{131}I was reduced according to the calculated RAIU ratio in that patient. This resulted in a dose reduction with a factor of 1.9 ± 0.5 (range, 1.2–2.6) in the 0.01-mg rhTSH group and of 2.4 ± 0.4 (range, 2.0–3.1) in the 0.03-mg rhTSH group (*P* < 0.05). ^{131}I doses were reduced from 68.9 ± 28.1 mCi (2550 ± 1041 MBq) to 39.4 ± 16.8 mCi (1457 ± 621 MBq) in the 0.01-mg rhTSH group and from 52.1 ± 33.3 mCi (1927 ± 1233 MBq) to 22.8 ± 5.7 mCi (843 ± 210 MBq) in the 0.03-mg rhTSH group.

Follow-up investigations

Effect of rhTSH administration on serum TSH levels (Fig. 2). After administration of 0.01 mg rhTSH, serum TSH rose from 0.68 ± 0.50 mU/liter (range, <0.03–1.70 mU/liter) to a peak of 4.49 ± 2.03 mU/liter (range, 2.20–9.80 mU/liter; *P** < 0.005). After administration of 0.03 mg rhTSH, serum TSH rose from 0.53 ± 0.54 mU/liter (range, <0.03–1.80 mU/liter) to a peak of 11.10 ± 2.59 mU/liter (range, 7.00–15.10 mU/liter; *P** < 0.01). Peak levels of serum TSH were significantly higher (*P* < 0.0001) after administration of 0.03 mg rhTSH than after administration of 0.01 mg rhTSH. In both groups, peak levels of serum TSH were reached at 5–8 h after administration of rhTSH. Thereafter, serum TSH declined rapidly; and, in all patients, a decrease in serum TSH below the baseline level was observed.

Short-term safety of rhTSH administration followed by ^{131}I therapy. Blood pressure, pulse rate, and body temperature were not significantly different at any time point until 84 d after ^{131}I treatment, compared with values immediately before rhTSH administration. No symptoms and signs of thyrotoxicosis, thyroiditis, (worsening of) tracheal compression, or other adverse effects were observed, either in the first 24 h after rhTSH administration or in the first 3 months after ^{131}I therapy.

Serum FT_4 and T_3 levels after rhTSH administration followed by ^{131}I therapy (Table 2). In the 0.01-mg rhTSH group, serum FT_4 rose from 15.8 ± 2.8 pM (range,

Table 1. *Baseline characteristics and results of ^{131}I therapy, 1 yr after pretreatment with a single dose of 0.01 mg (patients 1–12) or 0.03 mg (patients 13–22) rhTSH in 22 patients with nodular goiter*

Patient	Age (yr)	Thyroid volume[a] before ^{131}I (ml)	24-h RAIU baseline study (%)	24-h RAIU rhTSH study (%)	RAIU ratio[b]	Therapeutic dose of ^{131}I (mCi)	Thyroid volume[c]			SCAT[c]		
							Before ^{131}I (ml)	After ^{131}I (ml)	Decrease (%)	Before ^{131}I (cm²)	After ^{131}I (cm²)	Increase (%)
1	48	90	32	38	1.2	25.0	72	50	31	1.29	1.46	14
2	57	220	26	41	1.6	55.4	194	170	13	2.12	2.45	15
3	68	100	23	50	2.2	20.7	103	66	36	0.91	1.02	13
4	51	100	25	63	2.5	19.9	70	51	27	1.22	1.33	9
5	58	150	34	62	1.8	26.1	131	97	26	0.55	0.81	46
6	49	220	16	28	1.8	68.1	209	110	47	1.47	1.63	11
7	46	150	22	41	1.9	42.1	94	55	41	1.45	1.54	6
8	73	125	21	54	2.6	22.3	98	69	30	0.64	0.86	34
9	66	265	30	45	1.5	62.6	205	159	22	1.31	1.45	11
10	73	260	30	63	2.1	42.7	170	113	34	1.05	1.06	1
11	71	200	22	51	2.3	40.5	169	92	46	0.99	1.38	39
12	45	250	45	60	1.3	46.9	204	65	68	1.19	1.30	9
Mean ± SD	59 ± 11	178 ± 66	27 ± 8	50 ± 11	1.9 ± 0.5	39.4 ± 16.8	143 ± 54	91 ± 41	35 ± 14	1.18 ± 0.42	1.36 ± 0.43	17 ± 14
13	50	120	26	53	2.0	25.1	60	40	33	1.64	1.81	10
14	60	70	21	47	2.2	15.6	48	23	52	1.23	1.32	7
15	65	120	22	49	2.2	25.0	129	50	61	1.91	2.31	21
16	64	150	17	52	3.1	30.0	152	108	29	0.16	0.47	194
17	72	70	21	41	2.0	19.8	44	30	32	0.95	1.45	53
18	67	110	27	68	2.5	18.2	109	58	47	1.04	1.50	45
19	66	155	27	53	2.0	31.1	172	127	26	0.63	0.77	23
20	69	80	17	46	2.7	19.5	83	46	45	1.45	1.71	18
21	55	100	26	69	2.7	15.9	101	46	54	1.07	1.66	55
22	56	155	19	59	3.1	27.4	135	88	35	0.59	0.66	12
Mean ± SD	62 ± 7	113 ± 33	22 ± 4	54 ± 9	2.4 ± 0.4	22.8 ± 5.7	103 ± 44	62 ± 35	41 ± 12	1.07 ± 0.52	1.37 ± 0.58	44 ± 56
0.01-mg *vs.* 0.03-mg group	*P* = NS	*P* < 0.05	*P* = NS	*P* = NS	*P* < 0.05	*P* < 0.05	*P* = NS	*P* < 0.05	*P* = NS	*P* = NS	*P* = NS	*P* = NS

[a] Determined by scintigraphy.
[b] Twenty-four-hour RAIU rhTSH study/24-h RAIU baseline study.
[c] Determined by MRI.

11.4–20.7 pM) before rhTSH administration, to 17.7 ± 3.1 pM (range, 13.2-22.9 pM) immediately before ^{131}I therapy, *i.e.* 24 h after rhTSH administration (*P** < 0.005). Serum FT_4 levels at 2, 5, and 8 h after rhTSH administration were 15.8 ± 3.2 pM, 16.3 ± 3.1 pM, and 17.5 ± 2.9 pM, respectively. After ^{131}I administration, serum FT_4 levels increased further, to a peak level of 23.2 ± 4.4 pM (range, 16.2–32.4 pM; *P** < 0.005 *vs.* FT_4 levels immediately before ^{131}I administration; Fig. 2). Serum T_3 rose from 2.22 ± 0.38 nM (range, 1.80–2.90 nM) before rhTSH administration to 2.63 ± 0.42 nM (range, 1.90-3.40 nM) immediately before ^{131}I therapy (*P** < 0.005). Serum T_3 levels at 2, 5, and 8 h after rhTSH administration were 2.33 ± 0.49, 2.59 ± 0.45, and 2.73 ± 0.43 nM, respectively. After ^{131}I administration, serum T_3 increased further, to a peak level of 3.12 ± 0.58 nM (range, 2.60–4.60 nM; *P** < 0.005 *vs.* T_3 levels immediately before ^{131}I administration).

In the 0.03-mg rhTSH group, serum FT_4 rose from 15.5 ± 2.5 pM (range, 12.6–20.7 pM) before rhTSH administration to 20.4 ± 4.6 pM (range, 15.6-28.5 pM) immediately before ^{131}I therapy (*P** < 0.005). Serum FT_4 levels at 2, 5, and 8 h after rhTSH administration were 15.6 ± 2.2, 17.1 ± 2.7, and 18.3 ± 3.1 pM, respectively. After ^{131}I administration, serum FT_4 levels increased further, to a peak level of 23.5 ± 5.1 pM (range, 17.4-32.4 pM; *P** < 0.005 *vs.* FT_4 levels immediately before ^{131}I administration). Serum T_3 rose from 2.05 ± 0.36 nM (range, 1.60–2.80 nM) before rhTSH administration to 2.82 ± 0.72 nM (range, 1.90–4.50 nM) immediately before ^{131}I therapy (*P** < 0.005). Serum T_3 levels at 2, 5, and 8 h after rhTSH administration were 2.16 ± 0.42, 2.33 ± 0.57, and 2.73 ± 0.64 nM, respectively. After ^{131}I administration, serum T_3 increased further, to a peak level of 3.26 ± 0.82 nM (range, 2.20–4.70 nM; *P** < 0.005 *vs.* T_3 levels immediately before ^{131}I administration).

Individual peak FT_4 and T_3 levels were reached between 1 and 28 d after ^{131}I administration and were above the normal range in 12 (0.01-mg rhTSH group, n = 7; and 0.03-mg rhTSH group, n = 5) and 11 (0.01-mg rh TSH group, n = 5; and 0.03-mg rhTSH group, n = 6) patients, respectively.

TV and SCAT, 1 wk after ^{131}I therapy (Table 2). Before ^{131}I therapy, TV (as measured with MRI) was 143 ± 54 ml (range, 70–209 ml) in the 0.01-mg rhTSH group and 103 ± 44 ml (range, 44–172 ml) in the 0.03-mg rhTSH group [*P* = NS (not significant), 0.01 mg rhTSH *vs.* 0.03 mg rhTSH]. SCAT was 1.18 ± 0.42 cm^2 (range, 0.55–2.12 cm^2) in the 0.01-mg rhTSH group and 1.07 ± 0.52 cm^2 (range, 0.16–1.91 cm^2) in the 0.03-mg rhTSH group (*P* = NS, 0.01 mg rhTSH *vs.* 0.03 mg rhTSH).

One week after ^{131}I therapy, TV was 151 ± 61 ml (range, 74–240 ml) in the 0.01-mg rhTSH group and 114 ± 44 ml (range, 47–179 ml) in the 0.03-mg rhTSH group. Compared with the pretreatment TV, the increase of TV was 5% ± 8% (range, -6%–15%) in the 0.01-mg rhTSH group (*P** = NS) and 5% ± 6% (range,

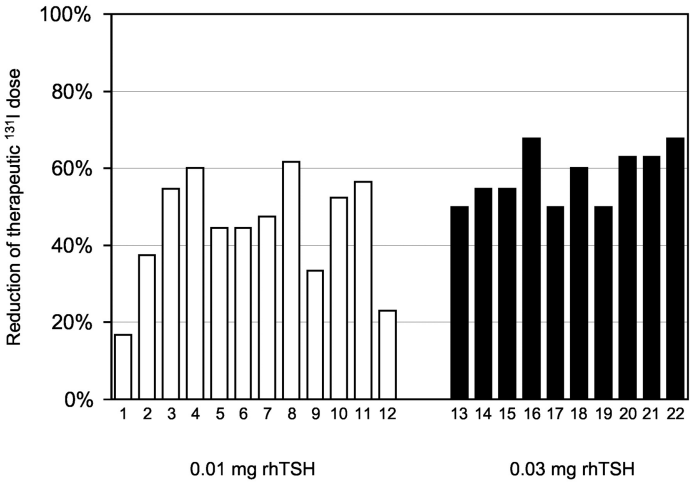


Figure 1. *Reduction of the therapeutic ^{131}I dose in the individual patients by pretreatment with 0.01 mg rhTSH (patients 1–12, □) or 0.03 mg rhTSH (patients 13–22, ■). In each patient, the therapeutic dose of ^{131}I was reduced according to the calculated RAIU ratio in that patient (RAIU ratio = ratio between 24-h RAIU after rhTSH and baseline 24-h RAIU, as determined before in diagnostic studies using tracer doses of ^{131}I).*

-4%–17%) in the 0.03-mg rhTSH group ($P^* < 0.05$). SCAT was 1.23 ± 0.50 cm^2 (range, 0.61–2.53 cm^2) in the 0.01-mg rhTSH group and 1.07 ± 0.58 cm^2 (range, 0.14–1.88 cm^2) in the 0.03-mg rhTSH group. In both groups, SCAT did not change significantly after 1 wk. Compared with the pretreatment SCAT, change of SCAT was 3% ± 8% (range, -13%–19%) in the 0.01-mg rhTSH group (P^* = NS) and 0% ± 9% (range, -11%–19%) in the 0.03-mg rhTSH group (P^* = NS).

Serum hs-CRP levels after rhTSH administration followed by ^{131}I therapy. In most patients, serum hs-CRP levels were undetectable both before and after ^{131}I therapy. Only in 1 patient in the 0.01-mg rhTSH group and in 1 patient in the 0.03-mg rhTSH group did hs-CRP levels exceed the upper level of the normal range after ^{131}I therapy (peak levels were 33.2 mg/liter at 7 d and 20.3 mg/liter at 10 d after ^{131}I therapy, respectively).

TV and SCAT, 1 yr after ^{131}I therapy (Table 1, Fig. 3). One year after ^{131}I treatment, TV was 91 ± 41 ml (range, 50–170 ml) in the 0.01-mg rhTSH group and 62 ± 35 ml (range, 23–127 ml) in the 0.03-mg rhTSH group. Compared with pretreatment TV, TV 1 yr after ^{131}I therapy was lower in all patients. Volume reduction after 1 yr was 35% ± 14% (range, 13%–68%) in the 0.01-mg rhTSH group ($P^* < 0.005$) and 41% ± 12% (range, 26%–61%) in the 0.03-mg rhTSH group ($P^* < 0.01$). TV reduction was not significantly different between the two groups.

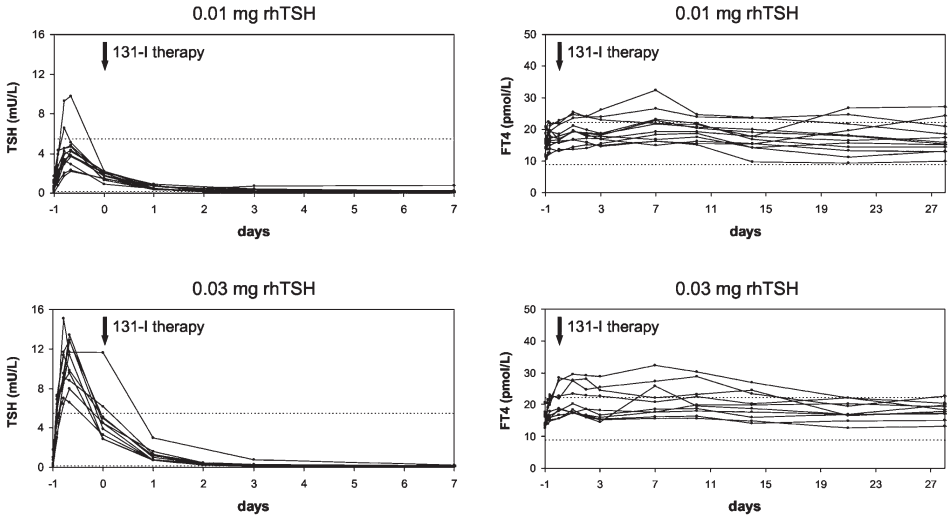


Figure 2. *Serum TSH levels (left) and FT_4 levels (right) before and after administration of 0.01 mg (top) and 0.03 mg (bottom) rhTSH, followed by an ^{131}I dose adjusted to the rhTSH-induced increase in 24-h RAIU, in 22 patients with nodular goiter; rhTSH was administered immediately after the first blood withdrawal at d -1, and ^{131}I was administered immediately after blood withdrawal at d 0. Dotted lines: upper and lower limits of the normal range for serum TSH and FT_4.*

One year after ^{131}I therapy, SCAT was 1.36 ± 0.43 cm^2 (range, 0.81–2.45 cm^2) in the 0.01-mg rhTSH group and 1.37 ± 0.58 cm^2 (range, 0.47–2.31 cm^2) in the 0.03-mg rhTSH group. Compared with pretreatment SCAT, the increase in SCAT after 1 yr was 17% ± 14% (range, 1%–46%) in the 0.01-mg rhTSH group (P^* < 0.005) and 44% ± 56% (range, 7%–194%) in the 0.03-mg rhTSH group (P^* < 0.01). The increase of SCAT was not significantly different between the two groups.

In the total group of 22 patients, there was no correlation between TV reduction and increase of SCAT (correlation coefficient = 0.12, P^{**} = NS). TV reduction achieved 1 yr after ^{131}I therapy was not significantly correlated with baseline TV (correlation coefficient = 0.09, P^{**} = NS).

Thyroid function after ^{131}I therapy. Serum levels of TRAbs became positive (>1.5 IU/liter) in four patients (0.01-mg rhTSH group, n = 3; and 0.03-mg rhTSH group, n = 1) 6 months after ^{131}I therapy. The individual peak levels were 2.8, 15.5, 4.1, and 2.2 IU/liter. Three of them (all in the 0.01-mg rhTSH group) developed symptoms and signs of hyperthyroidism between 23 and 25 wk after ^{131}I therapy. At the time of diagnosis of hyperthyroidism, serum TSH levels were less than 0.03 mU/liter, and serum FT_4 levels were 52.5, 58.0, and 35.7 pM.

Table 2. *Short-term safety parameters of ^{131}I therapy after pretreatment with a single dose of 0.01 mg (patients 1–12) or 0.03 mg (patients 13–22) rhTSH in 22 patients with nodular goiter*

Patient	Serum FT4 just before ^{131}I (pM)	Maximum serum FT4 after ^{131}I (pM)	Serum T3 just before ^{131}I (nM)	Maximum serum T3 after ^{131}I (nM)	Thyroid volume[a] change at 1 wk (%)	SCAT[a] change at 1 wk (%)
1	16.2	24.4	3.40	4.60	14	3
2	13.7	18.7	3.00	3.00	14	19
3	13.2	16.2	1.90	2.60	-5	9
4	17.1	22.9	2.60	2.60	6	2
5	21.5	26.6	2.70	3.10	9	9
6	15.7	27.1	2.40	3.40	15	-1
7	21.9	25.4	3.00	3.20	9	10
8	17.9	21.7	2.00	2.60	-3	1
9	18.6	23.3	2.40	2.90	13	-13
10	22.9	32.4	2.80	3.80	-6	-5
11	16.6	19.7	2.80	2.90	-2	2
12	16.6	19.5	2.50	2.80	-2	1
Mean ± SD	17.7 ± 3.1	23.2 ± 4.4[b]	2.63 ± 0.42	3.12 ± 0.58[b]	5 ± 8	3 ± 8
13	22.0	28.0	2.90	3.10	2	5
14	18.7	20.0	2.70	2.90	Not done	Not done
15	28.5	28.9	3.20	3.60	5	-1
16	22.7	23.5	2.10	2.20	1	-11
17	15.6	17.4	2.70	3.30	7	-3
18	27.5	32.4	4.50	4.50	17	19
19	16.8	20.3	1.90	2.30	4	-3
20	15.6	18.4	2.90	2.90	-4	4
21	18.1	20.2	3.00	3.10	1	2
22	18.6	25.8	2.30	4.70	6	-7
Mean ± SD	20.4 ± 4.6	23.5 ± 5.1[b]	2.82 ± 0.72	3.26 ± 0.82[b]	5 ± 6	0 ± 9
0.01-mg *vs.* 0.03-mg group	*P* = NS	*P* = NS	*P* = NS	*P* = NS	*P* = NS	*P* = NS

[a] Determined by MRI.

[b] *P** < 0.005, compared with serum values just before ^{131}I, *i.e.* 24 h after rhTSH administration.

In the year after ^{131}I therapy, L-thyroxine therapy was started in 8 patients (0.01-mg rhTSH group, n = 4; and 0.03-mg rhTSH group, n = 4) because, during follow-up, an elevated serum TSH level was measured. Pretreatment serum TSH levels were significantly ($P < 0.05$) higher in these 8 patients (0.99 ± 0.56 mU/liter; range 0.27–1.80 mU/liter) than in the other 14 patients (0.39 ± 0.31 mU/liter; range, <0.03–1.30 mU/liter). There was no significant difference in pretreatment TVs between the two groups. TV reduction tended to be higher ($P = 0.05$) in the patients in whom the serum TSH level became elevated during follow-up. Before therapy, anti-TPO antibodies were positive (>60 U/ml) in 3 patients of the total group. One year after therapy, anti-TPO antibodies were still positive in these 3 patients and had become positive in one other patient. There was no significant relation between the presence of anti-TPO antibodies and the development of an elevated serum TSH level: anti-TPO antibodies

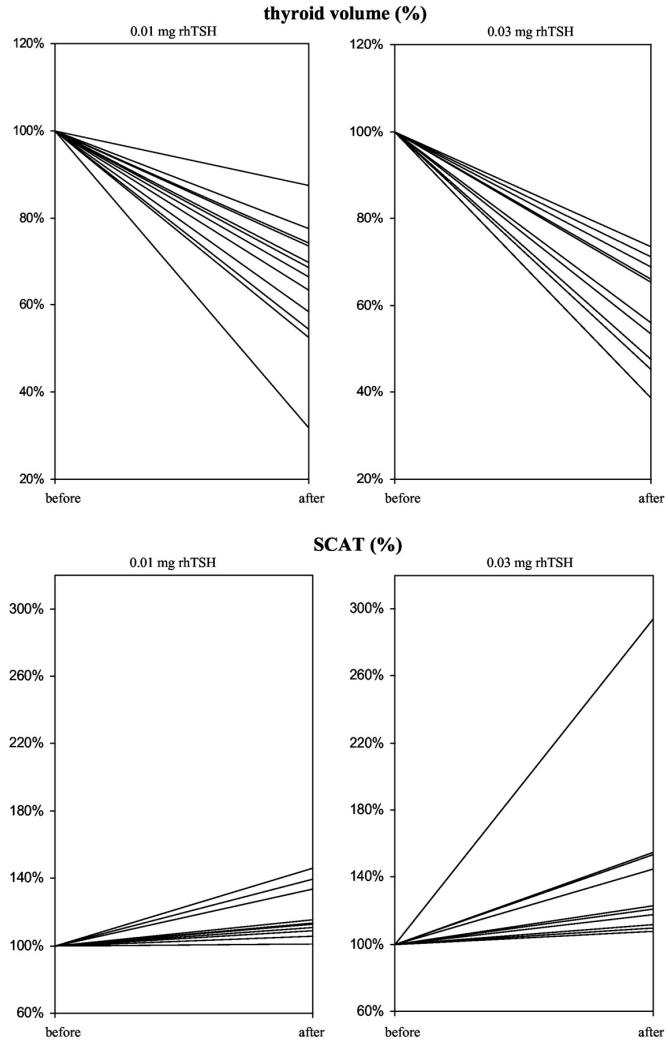


Figure 3. *TV (top), and SCAT (bottom) measured before and 1 yr after radioiodine therapy in 22 patients with nodular goiter who were pretreated with a single dose of rhTSH (0.01 mg, n = 12; or 0.03 mg, n = 10). The data are expressed as percentages of pretreatment values.*

were positive both before and 1 yr after ^{131}I therapy in 2 of the 8 patients, who started with L-thyroxine during the first year after ^{131}I therapy. In the other 6 patients in whom the serum TSH level became elevated during follow-up, anti-TPO antibodies were negative both before and 1 yr after therapy.

Discussion

In the present study, radioiodine therapy after pretreatment with a single, low dose of rhTSH in patients with nodular goiter resulted in a reduction in TV, 1 yr after therapy, of 35% (on average) in the group pretreated with 0.01-mg rhTSH group and of 41% (on average) in the group pretreated with 0.03 mg rhTSH. This was accompanied by an increase of the SCAT of 17% and 44% (on average), respectively. Although TV reduction and increase of the SCAT seemed to be better in the 0.03-mg rhTSH group than in the 0.01-mg rhTSH group, these differences were not statistically significant. Furthermore, initial goiter size in the 0.01-mg rhTSH group was approximately 40% greater than in the 0.03-mg rhTSH group, and this may have influenced the results of ^{131}I therapy, because the efficacy of ^{131}I therapy diminishes with increasing goiter size (19).

Our results are in line with those in earlier studies on TV reduction by radioiodine therapy in patients with nodular goiter, showing that radioiodine treatment results in a reduction of goiter volume by approximately 40% after 1 yr (3, 6, 7). In these studies, like in our study, single doses of approximately 100 μCi (3.7 MBq) ^{131}I per gram of thyroid tissue, corrected for the percentage uptake of radioiodine in the thyroid at 24 h, were given. However, an important difference between the present study and the earlier reports is that, in our study, pretreatment with rhTSH allowed reduction of the therapeutic dose of radioiodine by a factor of 1.9 (on average) in the group pretreated with 0.01 mg rhTSH and of 2.4 (on average) in the group pretreated with 0.03 mg rhTSH.

The radiation burden of radioiodine therapy to extrathyroidal organs is directly related to the dose of radioiodine administered (11). In our study, pretreatment with rhTSH allowed approximately 50–60% reduction of the therapeutic dose of radioiodine. Such a dose reduction may have important practical consequences. Until now, most clinicians have restricted radioiodine therapy for nontoxic, nodular goiter to elderly patients, especially those who have a high operative risk or refuse surgery. In these patients, the benefits of noninvasive radioiodine treatment outweigh the lifetime risk of this mode of therapy. However, because pretreatment with rhTSH may substantially lower the dose of radioiodine to be administered, this therapy may become more attractive for younger patients.

A main goal of the present study was to investigate the safety of the administration of a therapeutic dose of ^{131}I after pretreatment with rhTSH. We investigated whether pretreatment with a low dose of rhTSH did not exacerbate the mild increases in serum thyroid hormone levels and TV commonly seen after radioiodine treatment of nodular goiter (14). This proved to be not the case: only mild increases in serum FT_4 and T_3 were observed, and no symptoms and

signs of thyrotoxicosis occurred. Therefore, in our opinion, routine β blockade is not necessary.

In the 0.03-mg rhTSH group, a small increase in TV was observed 1 wk after ^{131}I therapy, but this was not accompanied by further narrowing of the tracheal lumen. We observed no symptoms or signs of thyroiditis in our patients, and serum CRP levels after radioiodine therapy did exceed the normal range in only 2 of the 22 patients. From our data, it seems that, in patients with nontoxic, nodular goiter, ^{131}I therapy after pretreatment with a low dose of rhTSH is safe.

In our study, three patients developed hyperthyroidism between 23 and 25 wk after ^{131}I therapy, which was accompanied by the presence of positive serum levels of TRAbs. Autoimmune hyperthyroidism may occur several months after radioiodine therapy for nontoxic, nodular goiter in approximately 5% of patients (20). It is of note that all three cases of autoimmune hyperthyroidism occurred in the group pretreated with the lowest dose of rhTSH, making a relationship with rhTSH pretreatment less likely.

In the year after ^{131}I therapy, L-thyroxine was started in eight patients, because, during follow-up, an elevated serum TSH level was measured. Reported incidences of posttreatment hypothyroidism after radioiodine therapy for nontoxic, nodular goiter in literature vary from 8–100% (1, 2, 4, 5, 6, 7, 19, 21). Nygaard *et al.* (2), using the life table method, calculated a cumulative risk of hypothyroidism of 22% at 5 yr after radioiodine treatment for small nontoxic goiters. However, in more recent studies, higher incidences were found, *e.g.* 22% after 1 yr (6) and 45% after 2 yr (7). Posttreatment hypothyroidism seems to be more common in patients with small goiters and in those with high pretreatment serum anti-TPO antibody concentrations (19). In our study, there was no correlation between the presence of anti-TPO antibodies before radioiodine treatment and the development of an elevated serum TSH level during follow-up, and there was no significant difference in pretreatment TV between patients who developed an elevated TSH level during follow-up and those who did not.

Our study has a number of limitations. First, it is an observational study, not a randomized trial comparing the safety and efficacy of ^{131}I therapy after pretreatment with different doses of rhTSH with that of standard ^{131}I therapy, *i.e.* without pretreatment with rhTSH. For this reason, our finding that a dose of 0.03 mg rhTSH resulted in a significantly higher increase in 24-h RAIU than a dose of 0.01 mg rhTSH has to be confirmed in a randomized setting. Second, it was not investigated whether doses of rhTSH higher than 0.03 mg rhTSH resulted in even higher increases of 24 h RAIU and whether pretreatment with such higher doses of rhTSH before radioiodine therapy is safe and more effective than pretreatment with the doses used in our study. Third, this study was

performed in an area with sufficient iodide intake. We cannot exclude that the effect of rhTSH pretreatment may be greater in areas with a higher iodide intake than in The Netherlands. Fourth, our study cannot answer the question of whether radioiodine therapy after pretreatment with rhTSH, but without diminishing the dose of ^{131}I according to the rhTSH-induced increase in 24-h RAIU, resulting in a higher radiation dose to the thyroid, may improve the effect of radioiodine therapy with respect to TV reduction.

In conclusion, pretreatment with a single, low dose of rhTSH in patients with nodular goiter allows a 50–60% reduction of the therapeutic dose of radioiodine without compromising the efficacy of TV reduction. Further studies are needed to assess whether treatment with larger doses of rhTSH and/or ^{131}I results in larger TV reduction in these patients.

References

1 **Hegedüs L, Hansen BM, Knudsen N, Hansen JM** 1988 Reduction of size of thyroid with radioactive iodine in multinodular non-toxic goitre. Br Med J 297:661–662

2 **Nygaard B, Hegedüs L, Gervil M, Hjalgrim H, Soe-Jensen P, Hansen JM** 1993 Radioiodine treatment of multinodular non-toxic goitre. Br Med J 307:828–832

3 **Huysmans DAKC, Hermus ARMM, Corstens FHM, Barentsz JO, Kloppenborg PWC** 1994 Large, compressive goiters treated with radioiodine. Ann Intern Med 121:757–762

4 **Wesche MF, Tiel-v Buul MM, Smits NJ, Wiersinga WM** 1995 Reduction in goiter size by ^{131}I therapy in patients with non-toxic multinodular goiter. Eur J Endocrinol 132:86–87

5 **de Klerk JMH, van Isselt JW, van Dijk A, Hakman ME, Pameijer FA, Koppeschaar HPF, Zelissen PMJ, van Schaik JPJ, van Rijk PP** 1997 Iodine-131 therapy in sporadic nontoxic goiter. J Nucl Med 38:372–376

6 **Bonnema SJ, Bertelsen H, Mortensen J, Andersen PB, Knudsen DU, Bastholt L, Hegedüs L** 1999 The feasibility of high dose iodine 131 treatment as an alternative to surgery in patients with a very large goiter: effect on thyroid function and size and pulmonary function. J Clin Endocrinol Metab 84:3636–3641

7 **Wesche MFT, Tiel-v Buul MMC, Lips P, Smits NJ, Wiersinga WM** 2001 A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. J Clin Endocrinol Metab 86:998–1005

8 **Huysmans D, Hermus A, Edelbroek M, Barentz J, Corstens F, Kloppenborg P** 1997 Radioiodine for nontoxic multinodular goiter. Thyroid 7:235–239

9 **Hermus AR, Huysmans DA** 1998 Treatment of benign nodular thyroid disease. N Engl J Med 338:1438–1447

10 **Nygaard B, Soes-Petersen U, Hoilund-Carlsen PF, Veje A, Holst PE, Vestergaard A, Solling K** 1996 Improvement of upper airway obstruction after ^{131}I-treatment of multinodular nontoxic goiter evaluated by flow volume loop curves. J Endocrinol Invest 19:71–75

11 **Huysmans DAKC, Buijs WCAM, van de Ven MTP, van den Broek WJM, Kloppenborg PWC, Hermus ARMM, Corstens FHM** 1996 Dosimetry and risk estimates of radioiodine therapy for large, multinodular goiters. J Nucl Med 37:2072–2079

12 **Huysmans DA, Nieuwlaat W-A, Erdtsieck RJ, Schellekens AP, Bus JW, Bravenboer B, Hermus AR** 2000 Administration of a single, low dose of recombinant human thyrotropin significantly enhances thyroid radioiodide uptake in nontoxic nodular goiter. J Clin Endocrinol Metab 85:3592–3596

13 **Nieuwlaat W-A, Hermus AR, Sivro-Prndelj F, Corstens FH, Huysmans DA** 2001 Pretreatment with recombinant human thyrotropin changes the regional distribution of radioiodine on thyroid scintigrams of nodular goiters. J Clin Endocrinol Metab 86:5330–5336

14 **Nygaard B, Faber J, Hegedüs L** 1994 Acute changes in thyroid volume and function following ^{131}I therapy of multinodular goitre. Clin Endocrinol (Oxf) 41:715–718

15 **DeGroot LJ** 1975 Graves' disease diagnosis and treatment. Multinodular goitre. In: DeGroot LJ, Stanbury JB, eds. The thyroid and its diseases. 4th ed. New York; Wiley: 314–367 and 637–665

16 **Doering P, Kramer K** 1958 Die Bestimmung des Schilddrüsengewichtes mit der Szintigraphie nach Gabe von Radiojod; Ein Beitrag zur Dosierung des Radioisotopes. Strahlenther 105:245–259

17 **Huysmans DAKC, de Haas MM, van den Broek WJM, Hermus ARMM, Barentsz JO, Corstens FHM, Ruijs SHJ** 1994 Magnetic resonance imaging for volume estimation of large multinodular goitres; a comparison with scintigraphy. Br J Radiol 67:519–523

18 **Rohrer F** 1915 Der Strömungswiderstand in den menschlichen Atemwegen und der EinfluB der unregelmäBigen Verzweigung des Bronchialsystems auf den Atmungsverlauf verscheidenen Lungenbezirken. Pflügers Arch ges Physiol 162:225–299

19 **Le Moli R, Wesche MFT, Tiel-van Buul MMC, Wiersinga WM** 1999 Determinants of long-term outcome of radioiodine therapy of sporadic non-toxic goitre. Clin Endocrinol (Oxf) 50:783–789

20 **Huysmans DAKC, Hermus ARMM, Edelbroek MAL, Tjabbes T, Oostdijk A, Ross HA, Corstens FHM, Kloppenborg PWC** 1997 Autoimmune hyperthyroidism occurring late after radioiodine treatment for volume reduction of large multinodular goiters. Thyroid 7:535–539

21 **Verelst J, Bonnyns M, Glinoer D** 1990 Radioiodine therapy in voluminous multinodular non-toxic goitre. Acta Endocrinol (Copenh) 122:417–421

4.2

Letter to the Editor and Authors' Response: Pretreatment with a Single, Low Dose of Recombinant Human Thyrotropin Allows Dose Reduction of Radioiodine Therapy in Patients with Nodular Goiter

Steen J. Bonnema, Viveque E. Nielsen, and Laszlo Hegedüs

Department of Endocrinology and Metabolism (S.J.B., V.E.N., L.H.), Odense University Hospital, Odense, Denmark

Willy-Anne Nieuwlaat, Dyde A. Huysmans, and Ad R. Hermus

Department of Nuclear Medicine (W.-A.N., D.A.H.), Catharina Hospital, Eindhoven; Department of Endocrinology (W.-A.N., A.R.H.), Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

The Journal of Clinical Endocrinology & Metabolism 2003; 88(12): 6113-6115

4.2

To the Editor:

We have with great interest read the paper by Nieuwlaat *et al.* (1). Their study and the recent one by Duick and Baskin (2), are the first demonstrating that recombinant human TSH (rhTSH) may be highly useful in relation to ^{131}I therapy for benign goiter. Nieuwlaat *et al.* (1) show that prestimulation with a very small amount of rhTSH (0.01 or 0.03 mg) in patients with a nontoxic nodular goiter allowed the ^{131}I activity to be halved, while still attaining a goiter reduction of approximately 40%. Such an effect of the ^{131}I therapy was to be expected, because the same group previously reported that an increased radioiodine uptake by the goiter can be obtained after rhTSH stimulation (3). However, before rhTSH stimulation is routinely used by clinicians to optimize the ^{131}I therapy in benign thyroid disorders, we wish to emphasize that several aspects with this combination have not yet been sufficiently enlightened. Furthermore, both studies (1, 2) have serious shortcomings.

Although the use of rhTSH has been extensively evaluated in the monitoring and therapy of differentiated thyroid cancer, complications may arise when patients with an intact thyroid function and/or goiter are stimulated with this agent. Although ^{131}I therapy is used routinely in some countries (*e.g.* Denmark and The Netherlands) for treatment of nontoxic goiter, this is clearly not the case in many parts of the world, as documented by recent questionnaire surveys (4). Additionally, the evidence for this strategy almost exclusively relies on uncontrolled studies (4). Therefore, before introducing a novel principle in this setting, indisputable evidence based on well-designed controlled trials should be provided. Unfortunately, no control group was included in the study by Nieuwlaat *et al.* (1) which predisposes to overlook confounding factors. For example, the goiter-reducing effect obtained by the ^{131}I therapy may have been blurred by a possible dependency on the pretreatment goiter volume, as described in other studies (4).

An issue largely overlooked is the fact that upper airway obstruction is present in a large fraction of patients with goiter, despite absence of symptoms (4). Some reports have suggested that stimulation with rhTSH causes significant swelling of tumor tissue in patients with papillary thyroid carcinoma (5, 6). It is plausible, but not proved, that a similar situation can occur in patients with a benign goiter. Considering that ^{131}I therapy in some cases causes a transient goiter growth (without prior rhTSH stimulation) of 15–25% within the first week (4), the combination with rhTSH may lead to severe tracheal compression resulting in acute respiratory distress in susceptible individuals. In the study by Nieuwlaat *et al.* (1), the goiter enlargement as well as the smallest tracheal cross-sectional area was estimated by magnetic resonance 1 wk after the ^{131}I therapy. On average, both structures were insignificantly altered, although a goiter growth up to 17% and a tracheal area reduction by 13% were observed (1). These figures are very similar to previous

findings by us (7). However, it is our experience that the thyroid gland in some individuals may respond profoundly to rhTSH stimulation *per se* by an acute enlargement of more than 100% (8). This appears within 48 h and is fortunately followed by a rapid reversion to normal size. Thus, it is possible that a transient but significant goiter increase in fact did occur immediately before or during the ^{131}I therapy in the study by Nieuwlaat *et al.* (1) but was overlooked because patients were scanned at the earliest 1 wk after therapy. It is reassuring that rhTSH stimulation in the low doses that were used in that study seemingly was well tolerated, but the number of patients was small (n = 22) and only few suffered from a goiter larger than 150 ml (1). Should it be confirmed that rhTSH stimulation may give rise to a significant acute thyroid enlargement, it must be investigated in detail whether this can be prevented successfully by *e.g.* corticosteroids or nonsteroid antiinflammatory drugs, as suggested by two recent reports (2, 8).

Besides this potential problem of goiter swelling and tracheal compression due to rhTSH stimulation, particularly in combination with ^{131}I therapy, other issues also need to be clarified. The aim in the study by Nieuwlaat *et al.* (1) was to reduce the ^{131}I activity through a higher rhTSH-induced radioiodine thyroid uptake. The average goiter reduction obtainable by ^{131}I therapy is 35–50% (4), which still may leave some patients with compressive symptoms, particularly those with large goiters. Although some studies have indicated a dose-relationship between ^{131}I and goiter reduction (4), this remains to be proven in a prospective controlled set-up. Because some areas in a goiter simply may not be susceptible to ^{131}I therapy due to inactive and degenerated nodular tissue, it may well be that the thyroid irradiation usually employed (approximately 100 Gy) is sufficient to obtain the maximum goiter reduction. Thus, it is presently an open question whether the goiter reduction can be amplified by the use of rhTSH prestimulation. A previous study by Nieuwlaat *et al.* (9) demonstrating a more homogenous distribution of ^{131}I in the nodular goiter after rhTSH stimulation holds promise in this setting. To estimate the impact of rhTSH stimulation on the thyroid irradiation, it would have been highly interesting if Nieuwlaat *et al.* (1) had measured the ^{131}I kinetics during the ^{131}I therapy of the patients with nontoxic multinodular goiter and compared data with a control group not receiving rhTSH prestimulation. Finally, the optimal dose of rhTSH remains to be determined. By using small amounts of rhTSH, thyrotoxicosis can be avoided in most individuals with an intact thyroid gland (1), but this must of course be balanced against the overall purpose of a sufficient increase of thyroid ^{131}I uptake.

Thus, evidence of a beneficial effect of rhTSH prestimulation awaits properly conducted randomized trials before routine use can be recommended. In addition, cost-benefit, optimum rhTSH dose, and most important, safety issues need to be clarified.

References

1 **Nieuwlaat WA, Huysmans DA, Van Den Bosch HC, Sweep CG, Ross HA, Corstens FH, Hermus AR** 2003 Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. J Clin Endocrinol Metab 88:3121–3129

2 **Duick DS, Baskin HJ** 2003 Utility of recombinant human thyrotropin for augmentation of radioiodine uptake and treatment of nontoxic and toxic multinodular goiters. Endocr Pract 9:204–209

3 **Huysmans DA, Nieuwlaat W, Erdtsieck J, Schellekens AP, Bus JW, Bravenboer B, Hermus AR** 2000 Administration of a single low dose of recombinant human thyrotropin significantly enhances thyroid radioiodine uptake in nontoxic nodular goiter. J Clin Endocrinol Metab 85:3592–3596

4 **Hegedüs L, Bonnema SJ, Bennedbaek FN** 2003 Management of simple nodular goiter: current status and future perspectives. Endocr Rev 24:102–132

5 **Braga M, Ringel MD, Cooper DS** 2001 Sudden enlargement of local recurrent thyroid tumor after recombinant human TSH administration. J Clin Endocrinol Metab 86:5148–5151

6 **Giovanni V, Arianna LG, Antonio C, Francesco F, Michele K, Giovanni S, Marco S, Giovanni L** 2002 The use of recombinant human TSH in the follow-up of differentiated thyroid cancer: experience from a large patient cohort in a single centre. Clin Endocrinol (Oxf) 56:247–252

7 **Bonnema SJ, Bertelsen H, Mortensen J, Andersen PB, Knudsen DU, Bastholt L, Hegedüs L** 1999 The feasibility of high dose iodine 131 treatment as an alternative to surgery in patients with a very large goiter: effect on thyroid function and size and pulmonary function. J Clin Endocrinol Metab 84:3636–3641

8 **Nielsen VE, Bonnema SJ, Hegedüs L** Effects of 0.9 mg recombinant human thyrotropin on thyroid size and function, in normal subjects. A randomized double-blind cross-over trial. Program of Annual Meeting of the European Thyroid Association, Edinburgh, UK, 2003 (Abstract 108)

9 **Nieuwlaat WA, Hermus AR, Sivro-Prndelj F, Corstens FH, Huysmans DA** 2001 Pretreatment with recombinant human TSH changes the regional distribution of radioiodine on thyroid scintigrams of nodular goiters. J Clin Endocrinol Metab 86:5330–5336

4.2

To the Editor:

We thank Dr. Bonnema and colleagues for their comments. Indeed, our study (1) is an observational study, not a randomized trial, comparing the safety and efficacy of ^{131}I therapy after treatment with various doses of recombinant human TSH (rhTSH) with that of standard ^{131}I therapy, *i.e.* without pretreatment with rhTSH. As Bonnema *et al.* emphasize, rhTSH administration in patients with nodular goiters might induce acute increases in serum thyroid hormone levels and thyroid size. At the start of our study, no data on this issue were available. Therefore, the principal aim of our study was to explore the short-term safety of the administration of a therapeutic dose of ^{131}I after pretreatment with a single dose of rhTSH. For safety reasons, we used low doses of rhTSH (0.01 or 0.03 mg), and we adjusted the therapeutic dose of ^{131}I to the rhTSH-induced increase in 24-h radioactive iodine uptake, as determined in a diagnostic study, using a tracer dose of ^{131}I. We did not aim at doses higher than 100 μCi (3.7 MBq) ^{131}I per gram of thyroid tissue retained at 24 h. We agree that thyroid volume measurements in the first few days after rhTSH administration would have been informative. However, because in our study a therapeutic dose of ^{131}I was given 24 h after rhTSH administration, radiation safety regulations in our hospital precluded such early measurements. Anyhow, we did not observe symptoms and signs of (worsening of) tracheal compression in the first days after rhTSH administration.

We fully agree with Bonnema *et al.* that further studies are needed before rhTSH can be advised as an adjunct to ^{131}I therapy in nodular goiter. First, it has to be determined in a formal dose-response study which dose of rhTSH is optimal for this purpose. This study is currently being performed in the United States. The optimal rhTSH dose should stimulate radioactive iodine uptake considerably, but should not cause unacceptable increases in serum thyroid hormone levels and thyroid volume. Then, radioiodine therapy with and without pretreatment with that particular dose of rhTSH should be investigated in randomized studies. Such studies should look carefully at dose-response relationships with respect to efficacy and adverse effects, especially when ^{131}I treatment with rhTSH prestimulation is intended to reach higher radiation-absorbed doses in the thyroid than in our study, with the aim of achieving larger volume reductions.

Reference

1 **Nieuwlaat WA, Huysmans DA, Van Den Bosch HC, Sweep CG, Ross HA, Corstens FH, Hermus AR** 2003 Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. J Clin Endocrinol Metab 88:3121–3129

chapter

5

5.1

Dosimetry of Radioiodine Therapy in Patients with Nodular Goiter After Pretreatment with a Single, Low Dose of Recombinant Human Thyroid-Stimulating Hormone

Willy-Anne Nieuwlaat, Ad R. Hermus, H. Alec Ross, Wilhelmina C. Buijs, Michela A. Edelbroek, Jo W. Bus, Frans H. Corstens, and Dyde A. Huysmans

---

Department of Nuclear Medicine (W.-A.N., M.A.E., J.W.B., D.A.H.), Catharina Hospital, Eindhoven;
Departments of Endocrinology (W.-A.N., A.R.H.), Chemical Endocrinology (H.A.R.), and Nuclear Medicine (W.C.B., F.H.C.), Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

The Journal of Nuclear Medicine 2004; 45(4):626-633

5.1

Abstract

A single, low dose of recombinant human thyroid-stimulating hormone (rhTSH) doubles 24-h RAIU and causes a more homogeneous distribution of radioiodine on thyroid scintigrams of patients with nodular goiter. Pretreatment with rhTSH allows the therapeutic dose of ^{131}I to be reduced by 50%–60% without compromising the result of thyroid volume reduction. The present study focused on the dosimetric aspects of therapy with a reduced dose of ^{131}I after pretreatment with rhTSH in patients with nodular goiter.

Methods: Thirty-six patients were treated with ^{131}I to reduce thyroid volume. Nine patients were pretreated with a single dose of 0.01 mg of rhTSH, and 9 patients, with 0.03 mg of rhTSH. Two control groups of 9 patients, matched for thyroid weight and 24-h radioactive iodide uptake, were not pretreated with rhTSH. The therapeutic dose of ^{131}I was aimed at being sufficient to result in retention of 3.7 MBq of ^{131}I per gram of thyroid tissue at 24 h. Thyroid radioactivity after ^{131}I administration was measured every 24 h for 3 d and on days 7, 10, 14, 21, and 28. A model of iodine biokinetics was used to estimate absorbed doses in organs. Protein-bound ^{131}I activity was measured at 1, 2, 3, 7, and 10 d and at 2, 3, and 4 wk after ^{131}I therapy.

Results: The administered activities were 1.5 times lower in the 0.01-mg rhTSH group and 1.9 times lower in the 0.03-mg rhTSH group than in the control groups. The absorbed dose in the thyroid was similar in the rhTSH-pretreated groups and in the control groups. In the organs of excretion (bladder) and uptake (stomach) of inorganic iodide, the absorbed doses were 2- to 3-fold lower in the pretreated groups than in the control groups. The effective dose equivalent outside the thyroid was considerably lower in the rhTSH-pretreated groups than in their respective control groups (1.6-fold in the 0.01-mg rhTSH group and 2.3-fold in the 0.03-mg rhTSH group). The time course of protein-bound ^{131}I activity in serum and the cumulated protein-bound ^{131}I activity in serum did not differ significantly between rhTSH-pretreated and control groups.

Conclusion: ^{131}I therapy after pretreatment with a single, low dose of rhTSH, with the dose reduced according to the rhTSH-induced increase in 24-h radioactive iodide uptake, caused lower radiation-absorbed doses in extrathyroidal organs and tissues, especially bladder and stomach, and no significant increase in the release of ^{131}I-labeled thyroid hormones into the circulation of patients with nodular goiter. Thus, this mode of therapy can be recommended, especially when the dose of radioiodine to be administered without rhTSH pretreatment is high.

Introduction

Radioiodine (^{131}I) therapy is effective for reduction of thyroid volume in patients with nontoxic, nodular goiter. Several studies have found that ^{131}I treatment decreased goiter size by approximately 40% after 1 y (1–7) and by 50%–60% after 3–5 y (2,8,9).

In the reported studies, a single dose of approximately 3.7 MBq (100 μCi) of ^{131}I per gram of thyroid tissue, corrected for thyroid radioactive iodide uptake (RAIU) at 24 h, was given. In patients with nontoxic, nodular goiter, RAIU is usually rather low. As a result, high doses of ^{131}I are often needed, causing a relatively high radiation burden to extrathyroidal tissues (10). Therefore, exploration of strategies to enhance RAIU in these patients would be of interest. A method to enhance RAIU in patients with nodular goiter is to increase the serum level of thyroid-stimulating hormone, which is often low normal or below normal.

In 2000, we reported that pretreatment with 0.01 or 0.03 mg of recombinant human thyroid-stimulating hormone (rhTSH) doubled 24-h RAIU in patients with nodular goiter (11). We also found that pretreatment with rhTSH caused a more homogeneous distribution of radioiodine on thyroid scintigrams of nodular goiters (12). Pretreatment with a single, low dose of rhTSH allowed us to reduce the therapeutic dose of radioiodine in patients with nodular goiter by 50%–60% without compromising the result of thyroid volume reduction (13).

The present study focused on the dosimetric aspects of therapy with a reduced dose of radioiodine after rhTSH pretreatment of patients with nodular goiter. We hypothesized that therapy with a reduced dose of ^{131}I after pretreatment with rhTSH would decrease the radiation burden to extrathyroidal tissues. Absorbed doses in the thyroid and in extrathyroidal organs and tissues were estimated for patients treated with radioiodine with and without rhTSH pretreatment, using thyroid radioactivity measurements and a model of iodine kinetics in the body as described by Robertson and Gorman (14).

Furthermore, we investigated whether pretreatment with rhTSH increased the release of ^{131}I-labeled thyroid hormones or thyroglobulin into the circulation after radioiodine therapy. If this were the case, the advantage of lowering the amount of free inorganic ^{131}I in the circulation by using lower therapeutic doses of ^{131}I after rhTSH pretreatment might be outweighed by an increase in circulating protein-bound ^{131}I levels (PB^{131}I).

Materials and Methods

Patients

Thirty-six patients with nodular goiter, who were referred for radioiodine therapy to reduce thyroid volume, participated in this study. All patients had normal serum levels of free thyroxine (9.0–22.3 pmol/L) and total triiodothyronine (1.0–3.0 nmol/L). Serum thyroid-stimulating hormone levels were normal (0.2–5.5 mU/L) in 24 patients and below normal in 12 patients. The results of careful palpation of the thyroid, followed by fine-needle aspiration biopsy of dominant nodules and of those that had a different consistency from other nodules within the gland gave no suggestion of thyroid malignancy in any of the patients. None of the patients had recently taken medication known to affect thyroid function or RAIU. Patients had not received iodine-containing agents in the last 6 mo. An electrocardiogram, complete blood count, liver enzyme determination, plasma creatinine and glucose measurement, and screening urinalysis did not show abnormalities in any patients.

Twenty-four hours before radioiodine therapy, a first group of 9 consecutive patients received 0.01 mg of rhTSH and a second group of 9 consecutive patients received 0.03 mg of rhTSH. Afterward, 18 consecutive patients were treated with radioiodine without rhTSH pretreatment; from these, 2 control groups of 9 patients each were selected, matching the rhTSH-pretreated groups with respect to thyroid weight and 24-h RAIU.

The institutional human research committee approved the study, and all patients gave written informed consent to participate.

Diagnostic investigations preceding radioiodine therapy

A diagnostic dose of 40 MBq of sodium (^{123}I) iodide was administered as an oral solution. RAIU, as a percentage of the administered dose of ^{123}I corrected for physical decay, was measured at 24 h using a 7.62 x 7.62 cm (3 x 3 in.) NaI (Tl) detector. Dead-time corrections were made using standard software. Thyroid scintigraphy in the 159-keV window of ^{123}I was performed 24 h after radioiodine administration. All thyroid scintigrams showed heterogeneous uptake.

In 18 patients, the influence of rhTSH on RAIU was investigated at least 2 wk after radioiodine administration for the baseline investigation. After reconstitution of 0.9 mg of freeze-dried rhTSH (Thyrogen ampules; Genzyme) with 1.2 mL of sterile water, part of the obtained solution was diluted with saline to a final concentration of 0.05 mg/mL. Immediately after dilution, 0.01 mg (0.2 mL; $n = 9$) or 0.03 mg (0.6 mL; $n = 9$) of rhTSH was injected in the quadriceps muscle. Twenty-four hours after the administration of rhTSH, a diagnostic dose of 40 MBq of sodium ^{123}I was administered as an oral solution. RAIU, as a percentage of the administered dose of ^{123}I corrected for physical decay, was measured at 24 h.

Radioiodine therapy

Twenty-three days (median; range, 5–84 d) after the last diagnostic 24-h RAIU measurement, radioiodine therapy was given as a single oral dose to all 36 patients on an in-patient basis. The therapeutic dose of ^{131}I was aimed at being sufficient to result in retention of 3.7 MBq (100 μCi) of ^{131}I per gram of thyroid tissue at 24 h, according to the following formula: administered activity (GBq) = [thyroid weight (g) x 0.37 (GBq/g)]/24-h thyroid RAIU (%) (15). Thyroid weight was estimated from the planimetric surface on the baseline scintigram using the formula of Doering and Kramer (16): thyroid weight (g) = 0.326 x surface $(cm^2)^{3/2}$.

The 18 patients who were treated with rhTSH before radioiodine therapy again received an injection of rhTSH in the quadriceps muscle, using the same rhTSH dose as was given for the diagnostic investigation. The therapeutic dose of radioiodine was given 24 h later. In the rhTSH-pretreated patients, the therapeutic dose of ^{131}I was adjusted to the 24-h RAIU after rhTSH pretreatment, as determined for the individual patients in the preceding diagnostic investigations. The RAIU ratio is defined as the ratio between the 24-h RAIU after rhTSH pretreatment and the baseline 24-h RAIU (Table 1). Neither group of 9 control patients received rhTSH pretreatment.

Thyroid radioactivity measurements and dosimetric calculations

In all 36 patients, thyroid radioactivity was measured every 24 h for 3 d after the administration of the therapeutic dose of radioiodine and on days 7, 10, 14, 21, and 28. A 7.62 x 7.62 cm (3 x 3 in.) NaI (Tl) detector was used, with a lead shield placed in front of it to reduce the counting rate and avoid dead-time effects. Measurements were corrected for a standard with a known activity of ^{131}I, and all values were corrected for background radioactivity and for physical decay.

Thyroid radioactivity measurements were implemented in a simplified model for iodine biokinetics as described by Robertson and Gorman (14), with some amendments, as previously described by Huysmans et al. (10). Serum creatinine levels were within the reference range in all patients. Therefore, a normal urinary excretion rate of radioiodide was assumed for all patients (17). The rate of uptake of radioiodine into the thyroid was calculated from the radioactivity measurements at 24 h and from the radioiodide excretion rate. The fractional excretion of radioiodinated thyroid hormones from the thyroid into the circulation was calculated from thyroid radioactivity measurements from day 2 onward, fitted as a monoexponential function.

Radiation-absorbed doses in organs were calculated using the MIRD method (18). The calculated cumulated fractional activities in the source organs thyroid, urinary bladder, stomach, small intestine, and total body were entered in the MIRDOSE3.1 computer program (Oak Ridge Institute for Science and Education).

Absorbed doses in the thyroid were corrected for the ratio of normal thyroid weight (20 g) to individual thyroid weight estimated by thyroid scintigraphy. Tissue weighting factors were used to determine the effective dose equivalent outside the thyroid (19).

Hormone assays

Free thyroxine and total triiodothyronine were measured by chemiluminescent immunoassay and serum thyroid-stimulating hormone by 2-site immunochemiluminometric assay using an ACS:180 Automated Chemiluminescence System (Bayer).

PB^{131}I measurements

Blood samples were drawn from all patients at 1, 2, 3, 7, and 10 d and at 2, 3, and 4 wk after radioiodine administration. From each serum sample, 0.3 mL was taken for measurement of total ^{131}I activity in the serum and 0.3 mL for measurement of PB^{131}I activity. The latter 0.3-mL sample was prediluted with 0.9 mL of a solution of 0.05 mol/L phosphate buffer (pH 7.4) and 0.1 mol/L sodium chloride. Protein-bound iodine was precipitated by addition of 1.5 mL of cold trichloroacetic acid, 20%. The resulting samples were left standing for 10 min at room temperature and then centrifuged for 2 min at 2,000 rpm. The precipitate was washed twice with the trichloroacetic acid solution. By this method, 89% ± 6% of the total serum free thyroxine is precipitated (H.A. Ross, unpublished data, 1999). All samples (total serum and precipitate) were measured in a universal γ-counter (1282 Compugamma CS; Wallac). Radioactivity in all samples was compared with a standard curve of sodium-^{131}I with known activity, to calculate the activity in MBq/L.

Time–activity curves were created for total ^{131}I activity and PB^{131}I activity in each individual patient (Fig. 1). The area under each PB^{131}I time–activity curve was calculated. This area under the curve represents the cumulated PB^{131}I activity in each serum fraction and is expressed in GBq·L^{-1}·d. The cumulated total ^{131}I activity in the serum was not calculated because, in view of radiation safety regulations in the hospital, measurements on the day of radioiodine therapy had not been performed and because total ^{131}I activity in the serum is highest in the first hours after radioiodine administration, in contrast to PB^{131}I activity, which is low during the first day after radioiodine therapy.

Statistical analyses

The mean value ± SD is given, unless otherwise stated. Statistical analyses were done using the Mann–Whitney *U* test (with probability values denoted as *P*) and the Spearman rank correlation test (with probability values denoted as *P**). Areas under the time–activity curves obtained from the subjects who received rhTSH were compared with those of the matched controls by means of the Mann–Whitney *U* test. The time–activity curves themselves were compared by repeated-measures ANOVA, with time after ^{131}I administration as the within-subject factor and rhTSH pretreatment as the between-subjects factor. Probability values < 0.05 were considered to indicate statistical significance.

Results

Table 1 shows the characteristics of all patients and the data on their thyroid radioactivity measurements. As expected, because rhTSH-pretreated groups and control groups were matched for thyroid weight and thyroid 24-h RAIU, thyroid weight, based on planimetric thyroid scintigrams, and baseline thyroid 24-h RAIU were similar in the rhTSH groups and their respective control groups. rhTSH-stimulated 24-h RAIU in the pretreated groups was considerably higher than baseline RAIU in the control groups. Therefore, the average administered activities in the rhTSH-pretreated groups were considerably lower than those in the control groups (in the 0.01-mg rhTSH group, 67% of that in the control group; in the 0.03-mg rhTSH group, 53% of that in the control group; both $P < 0.05$).

Thyroid radioactivity measurements after radioiodine therapy showed somewhat lower 24-h RAIU of the therapeutic doses when compared with the 24-h RAIU of the previous diagnostic doses. However, this trend was observed not only in the rhTSH-pretreated groups but also in the control groups (Table 1). The effective half-time of ^{131}I in the thyroid did not significantly differ between rhTSH-pretreated patients and control patients (Table 1). The cumulated fractional activity (MBq·h/administered MBq) in the thyroid was approximately 1.7 times higher in the 0.01-mg rhTSH-pretreated group and 2.2 times higher in the 0.03-mg rhTSH-pretreated group than in their respective control groups (Table 1). The cumulated fractional activity in the liver, as calculated from thyroid radioactivity measurements and the biokinetic model (14) with modifications (10), was also longer in the pretreated groups, because their higher thyroid RAIU caused the component of radioiodinated thyroid hormones to be larger. Cumulated fractional activities in the other source organs, mainly determined by inorganic iodide (stomach, small intestine, rest of body, urinary bladder), were significantly lower in the rhTSH-pretreated patients (0.01 mg and 0.03 mg rhTSH) than in their controls.

Table 2 shows the calculated absorbed doses in the tissues and organs for which a tissue-weighting factor has been determined (19), expressed as dose per unit of administered radioiodine (in mGy/MBq) and as dose resulting from the total administered activities of radioiodine (in Gy). The absorbed dose in the thyroid per unit of administered activity was higher in the pretreated groups than in the control groups because of the higher cumulated fractional activity in the thyroid of the pretreated groups.

Outside the thyroid gland, the highest absorbed doses calculated per megabecquerel of administered ^{131}I were in urinary bladder, followed by the stomach. For these organs, the absorbed doses per megabecquerel were significantly higher without than with rhTSH pretreatment ($P < 0.0001$). Absorbed doses per megabecquerel of administered radioiodine inversely correlated with 24-h RAIU for the urinary bladder ($r = -0.73$; $P^* < 0.0001$) and the stomach ($r = -0.74$; $P^* <$

0.0001). Absorbed doses per megabecquerel of administered radioiodine in some of the other target organs (bone surface, breast, lungs, red bone marrow, and skin) were determined predominantly by the cumulated fractional activity in the thyroid and were therefore higher in the pretreated groups than in the control groups.

The absorbed dose in the thyroid resulting from the total administered activity was similar in the pretreated groups and their respective control groups. Outside the thyroid, the highest absorbed doses resulting from the total administered activities were in the urinary bladder and the stomach. In these organs of excretion (bladder) and uptake (stomach) of inorganic iodide, the absorbed doses resulting from the total administered activity were 2- to 3-fold lower in the pretreated groups than in their control groups. In all other extrathyroidal organs and tissues, somewhat lower absorbed doses were found in the pretreated groups than in the control groups, but the differences did not reach significance, except for those in colon and gonads.

The effective dose equivalent for the combined organs and tissues outside the thyroid gland was considerably lower in the rhTSH-pretreated groups than in their control groups (0.01-mg rhTSH group vs. control group, 0.21 ± 0.09 Gy vs. 0.33 ± 0.10 Gy [$P < 0.05$]; 0.03-mg rhTSH group vs. control group, 0.12 ± 0.03 Gy vs. 0.27 ± 0.14 Gy [$P < 0.05$]).

The cumulated $PB^{131}I$ activity in serum did not differ significantly between pretreated groups and their respective control groups. The cumulated $PB^{131}I$ activity in serum was 0.93 ± 0.15 GBq·L^{-1}·d in the 0.01-mg rhTSH group versus 0.70 ± 0.13 GBq·L^{-1}·d in the control group and 0.85 ± 0.12 GBq·L^{-1}·d in the 0.03-mg rhTSH group versus 0.52 ± 0.13 GBq·L^{-1}·d in the control group (mean value ± SEM; $n = 9$). Figure 1 shows the time–activity curves of total ^{131}I activity and $PB^{131}I$ activity in serum after radioiodine therapy in the 2 groups of rhTSH-pretreated patients and in the 2 control groups. The time course of $PB^{131}I$ activities did not significantly differ between pretreated and control groups.

Table 1. *Patient Characteristics and Results of Radioactivity Measurements After Radioiodine Treatment With and Without rhTSH Pretreatment of Patients with Nodular Goiter*

Characteristic	0.01 mg rhTSH			0.03 mg rhTSH		
	Treatment	Control	*P*	Treatment	Control	*P*
No. of patients	9	9		9	9	
Age (y)	57 ± 9 (46-71)	65 ± 8 (56-82)	NS	62 ± 7 (50-72)	64 ± 9 (54-82)	NS
Female-to-male ratio	7:2	9:0		7:2	9:0	
Baseline serum TSH (mU/L)	0.73 ± 0.46 (0.27-1.70)	0.45 ± 0.47 (0.03-1.32)	NS	0.55 ± 0.56 (0.03-1.80)	0.69 ± 0.84 (0.03-2.44)	NS
Thyroid weight (g)[a]	166 ± 63 (90-265)	161 ± 51 (85-225)	NS	117 ± 33 (70-155)	114 ± 59 (45-190)	NS
24-h RAIU baseline (%)	26 ± 6 (16-34)	29 ± 7 (20-43)	NS	23 ± 4 (17-27)	26 ± 5 (20-36)	NS
24-h RAIU rhTSH (%)	47 ± 11 (28-63)	Not done		55 ± 9 (41-69)	Not done	
RAIU ratio	1.9 ± 0.4 (1.2-2.5)	Not done		2.4 ± 0.4 (2.0-3.1)	Not done	
Therapeutic dose of ^{131}I (GBq)	1.5 ± 0.7 (0.7-2.5)	2.2 ± 0.7 (1.1-3.0)	<0.05	0.9 ± 0.2 (0.6-1.1)	1.7 ± 0.9 (0.6-3.0)	<0.05
24-h RAIU therapeutic dose (%)	45 ± 6 (37-54)	25 ± 7 (16-39)	<0.0001	49 ± 8 (42-66)	22 ± 5 (15-27)	<0.0001
Effective half-time of ^{131}I in thyroid (d)	6.4 ± 0.6 (5.2-7.1)	6.4 ± 0.3 (6.0-6.7)	NS	6.6 ± 0.5 (5.8-7.2)	6.4 ± 0.2 (6.0-6.7)	NS
Biologic half-time of ^{131}I in thyroid (d)	36 ± 15 (14-58)	32 ± 6 (23-39)	NS	41 ± 18 (21-73)	33 ± 6 (23-40)	NS
Cumulated activity in thyroid (GBq x h)	145 ± 61 (67-223)	126 ± 41 (62-177)	NS	95 ± 20 (63-120)	86 ± 37 (35-137)	NS
Cumulated fractional activity of ^{131}I in						
• Thyroid (h)[b]	100.18 ± 14.77 (72.28-116.79)	58.78 ± 13.96 (37.65-83.45)	<0.0001	114.18 ± 22.96 (90.68-165.13)	51.97 ± 9.87 (37.65-63.58)	<0.0001
• Stomach (h)[c]	1.11 ± 0.09 (0.97-1.23)	1.46 ± 0.13 (1.20-1.63)	<0.0001	1.00 ± 0.15 (0.69-1.14)	1.53 ± 0.09 (1.43-1.65)	<0.0001
• Small intestine (h)[c]	1.25 ± 0.11 (1.10-1.39)	1.66 ± 0.15 (1.36-1.85)	<0.0001	1.14 ± 0.18 (0.78-1.30)	1.73 ± 0.10 (1.62-1.87)	<0.0001
• Liver (h)[c]	0.45 ± 0.14 (0.30-0.70)	0.28 ± 0.10 (0.16-0.51)	<0.01	0.45 ± 0.16 (0.29-0.76)	0.24 ± 0.06 (0.14-0.31)	<0.001
• Rest of body (h)[c]	5.67 ± 0.46 (5.13-6.52)	7.04 ± 0.47 (6.20-7.73)	<0.0001	5.22 ± 0.73 (3.60-5.97)	7.27 ± 0.33 (6.89-7.73)	<0.0001
• Urinary bladder (h)[c]	1.31 ± 0.10 (1.20-1.50)	1.60 ± 0.09 (1.43-1.74)	<0.0001	1.22 ± 0.16 (0.87-1.38)	1.64 ± 0.07 (1.56-1.74)	<0.0001

a Determined by scintigraphy.
b Calculated from thyroid radioactivity measurements.
c Calculated using thyroid radioactivity measurements and the biokinetic model of Robertson and Gorman, with amendments based on MIRD Pamphlet No. 12 and MIRD Report No. 5.
NS = not statistically significant.
Data are mean ± SD, with ranges in parentheses.

Discussion

Our study, based on thyroid radioactivity measurements and the iodine biokinetic model of Robertson and Gorman (14), shows that radioiodine therapy after pretreatment with rhTSH, with the dose of ^{131}I reduced according to the rhTSH-induced increase in 24-h RAIU, caused a lower radiation burden to the extrathyroidal tissues than did radioiodine therapy without rhTSH pretreatment in patients with nodular goiter. The reduction in radiation burden was largest for the urinary bladder and the stomach. These are the extrathyroidal organs that receive the highest radiation doses from radioiodine therapy.

The therapeutic ^{131}I doses given to the rhTSH-pretreated patients were reduced according to the individual increases in diagnostic 24-h RAIU after rhTSH administration. RAIU measurements after therapy showed that the 24-h RAIU of the therapeutic dose was somewhat lower than the 24-h RAIU of the preceding diagnostic dose in most patients. However, this occurred in all 4 groups of patients to a similar degree, and the 24-h RAIU of the therapeutic dose was considerably higher in the rhTSH-pretreated groups than in the control groups. The effective half-time of

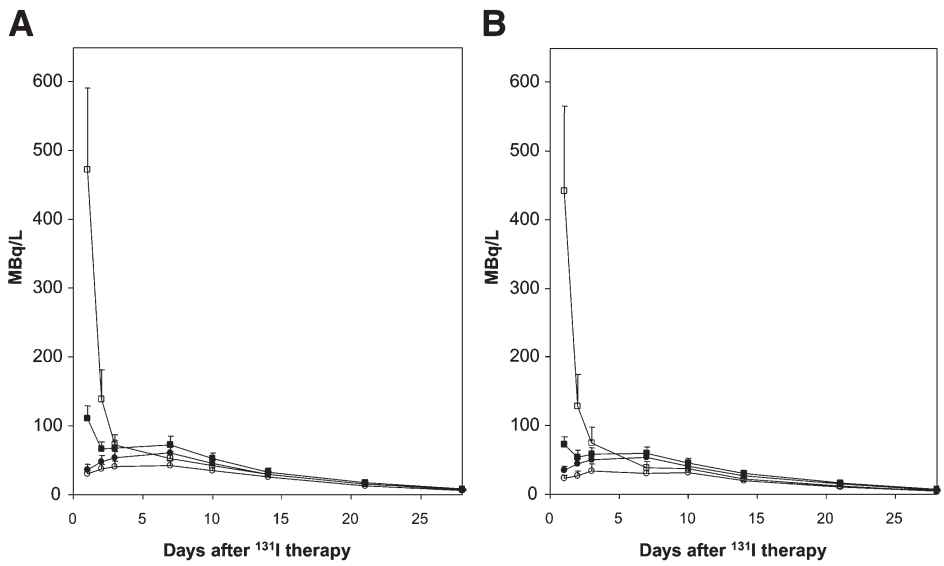


Figure 1. *Total ^{131}I activity and $PB^{131}I$ activity per liter of serum on day 0 after radioiodine therapy in patients with nodular goiter. (A and B) Nine patients were pretreated with 0.01 mg of rhTSH (A), and 9 with 0.03 mg of rhTSH (B). The results for each rhTSH group were compared with those for 9 control patients. Mean value + SEM is given. ■ = total ^{131}I activity in rhTSH-pretreated patients; □ = total ^{131}I activity in control patients; ● = $PB^{131}I$ activity in rhTSH-pretreated patients; ○ = $PB^{131}I$ activity in control patients.*

Table 2. *Radiation-Absorbed Doses in Target Organs After Radioiodine Treatment With and Without rhTSH Pretreatment in Patients with Nodular Goiter*

	Absorbed dose per unit administered activity (mGy/MBq)					
	0.01 mg rhTSH			0.03 mg rhTSH		
Target organ	Treatment	Control	*P*	Treatment	Control	*P*
Thyroid[a]	92.60 ± 42.72	54.24 ± 19.59	<0.05	139.40 ± 55.76	82.60 ± 48.84	<0.05
Bone surface	0.17 ± 0.02	0.11 ± 0.02	<0.0001	0.18 ± 0.03	0.11 ± 0.01	<0.0001
Breast	0.06 ± 0.01	0.05 ± 0.01	<0.05	0.07 ± 0.01	0.05 ± 0.00	<0.0001
Colon[b]	0.05 ± 0.01	0.06 ± 0.00	<0.0001	0.07 ± 0.09	0.06 ± 0.00	<0.005
Liver	0.07 ± 0.02	0.05 ± 0.01	<0.05	0.07 ± 0.01	0.05 ± 0.01	<0.0001
Lungs	0.13 ± 0.02	0.09 ± 0.01	<0.001	0.15 ± 0.03	0.09 ± 0.01	<0.0001
Ovaries	0.05 ± 0.00	0.06 ± 0.00	<0.0001	0.04 ± 0.01	0.06 ± 0.00	<0.0001
Red bone marrow	0.12 ± 0.02	0.09 ± 0.01	<0.0001	0.13 ± 0.02	0.08 ± 0.01	<0.0001
Skin	0.12 ± 0.04	0.09 ± 0.02	NS	0.13 ± 0.04	0.08 ± 0.01	<0.05
Stomach	0.34 ± 0.03	0.45 ± 0.04	<0.0001	0.31 ± 0.05	0.47 ± 0.02	<0.0001
Testes	0.02 ± 0.00			0.02 ± 0.00		
Urinary bladder	0.55 ± 0.08	0.71 ± 0.04	<0.0001	0.51 ± 0.09	0.73 ± 0.03	<0.0001
Remainder[c]	0.10 ± 0.01	0.10 ± 0.00	NS	0.11 ± 0.02	0.09 ± 0.00	<0.05
EDE outside thyroid (Sv)						

[a] Thyroid absorbed doses as calculated with MIRDOSE3.1 are corrected for the ratio of normal thyroid weight (20 g) to measured actual thyroid weight determined by scintigraphy.

[b] 0.57 x dose to upper large intestine + 0.43 x dose to lower large intestine.

[c] The absorbed dose in the remainder of the body is the average dose in the following organs and tissues: adrenals, brain, upper large intestine, small intestine, kidney, muscle, pancreas, spleen, thymus, and uterus.

EDE = effective dose equivalent.

Data are mean ± SD (n = 9 patients in each group).

Absorbed dose (Gy)					
0.01 mg rhTSH			0.03 mg rhTSH		
Treatment	Control	*P*	Treatment	Control	*P*
113.41 ± 16.30	107.42 ± 12.69	NS	108.94 ± 15.52	109.75 ± 23.25	NS
0.24 ± 0.09	0.25 ± 0.08	NS	0.15 ± 0.03	0.19 ± 0.10	NS
0.09 ± 0.04	0.11 ± 0.03	NS	0.06 ± 0.01	0.09 ± 0.04	NS
0.07 ± 0.03	0.13 ± 0.04	<0.005	0.06 ± 0.07	0.11 ± 0.06	<0.05
0.10 ± 0.04	0.11 ± 0.03	NS	0.06 ± 0.02	0.08 ± 0.04	NS
0.19 ± 0.07	0.21 ± 0.06	NS	0.12 ± 0.03	0.15 ± 0.08	NS
0.06 ± 0.03	0.13 ± 0.04	<0.01	0.04 ± 0.01	0.10 ± 0.05	<0.01
0.17 ± 0.07	0.19 ± 0.06	NS	0.11 ± 0.02	0.15 ± 0.08	NS
0.17 ± 0.07	0.20 ± 0.06	NS	0.11 ± 0.03	0.15 ± 0.08	NS
0.50 ± 0.24	0.99 ± 0.33	<0.005	0.27 ± 0.09	0.81 ± 0.43	<0.001
0.05 ± 0.00			0.02 ± 0.00		
0.80 ± 0.37	1.55 ± 0.50	<0.005	0.44 ± 0.16	1.27 ± 0.66	<0.005
0.14 ± 0.06	0.21 ± 0.06	<0.05	0.09 ± 0.02	0.17 ± 0.09	NS
0.21 ± 0.09	0.33 ± 0.10	<0.05	0.12 ± 0.03	0.27 ± 0.14	<0.05

radioiodine in the thyroid did not differ significantly between pretreated and control groups. Therefore, although we calculated increased absorbed doses in the thyroid per unit of administered activity in the pretreated groups, the total absorbed doses in the thyroid were similar in the rhTSH-pretreated groups and their respective control groups. Thyroid volume reduction by radioiodine has been shown to correlate positively with the administered amount of radioiodine per gram of thyroid tissue corrected for 24-h RAIU (5) and consequently with the absorbed dose in the thyroid. Therefore, reducing the therapeutic dose of radioiodine after rhTSH administration is not likely to have negatively influenced thyroid volume reduction. This is in accordance with recently published data by our group (13).

We used the MIRDOSE3.1 program to calculate the doses that extrathyroidal tissues absorbed from the total administered activity of radioiodine. Extrathyroidally absorbed doses after radioiodine therapy were by far highest in the urinary bladder and stomach, as was expected because inorganic iodine is excreted through the bladder and is concentrated (although not made organic) in the stomach. Enhanced uptake of radioiodine in the thyroid of rhTSH-pretreated patients resulted in lower amounts of circulating inorganic radioiodine during the first days after therapy and in lower cumulated fractional activities of radioiodine in the inorganic radioiodine compartment (including the stomach) and the bladder. Therefore, the absorbed doses in urinary bladder and stomach were reduced by a factor of 2 in the 0.01-mg rhTSH group and by a factor of 3 in the 0.03-mg rhTSH group in comparison with their respective control groups. These reductions are important, because the risk of cancer of the stomach has been reported to be slightly increased after radioiodine therapy in patients with toxic, nodular goiter (20,21). In other studies, the incidences of bladder cancer and breast cancer have been reported to be increased in patients with toxic nodular goiter treated with radioiodine (22–24).

The liver is the organ in which ^{131}I incorporated in thyroid hormones is collected and metabolized. This was accounted for by assigning 40% of the extrathyroidal thyroid hormone compartment to the liver. The amount of ^{131}I-labeled thyroid hormone per megabecquerel of radioiodine administered was higher in the rhTSH-pretreated groups than in the control groups, resulting in a higher cumulated fractional activity of ^{131}I in the liver in the rhTSH-pretreated groups. However, the absorbed dose in the liver was similar in rhTSH-pretreated and control groups because of the reduction in administered dose of radioiodine in the rhTSH-pretreated groups.

Absorbed doses in all extrathyroidal organs were lower in the rhTSH-pretreated groups than in the control groups. However, in the organs, in which the absorbed dose is predominantly determined by the cumulated activity in the thyroid, the difference did not reach statistical significance, because the cumulated activity in

the thyroid was similar in rhTSH-pretreated and control groups. The effective dose equivalent outside the thyroid was considerably lower in the rhTSH-pretreated groups than in their respective control groups (1.6-fold in the 0.01-mg rhTSH group and 2.3-fold in the 0.03-mg rhTSH group).

Not only thyroid iodine uptake but also thyroid hormone release is stimulated by thyroid-stimulating hormone. Thyroid stimulation predominantly releases thyroid hormones incorporating iodine that was recently taken up, not iodine that was stored for a longer time (last-come, first-served principle of thyroid iodine release) (25). Therefore, it might be that the administration of rhTSH before radioiodine therapy increases the release of radiolabeled thyroid hormones from the thyroid into the circulation. It has been argued that such an increase in radiolabeled thyroid hormones in the serum ($PB^{131}I$) might outweigh the advantage of a reduction in radioiodine dose after rhTSH pretreatment (26). Our measurements were reassuring, because no significant difference in the time course of circulating $PB^{131}I$ levels was observed between the rhTSH-pretreated groups and the control groups and because the cumulated $PB^{131}I$ activities did not differ significantly between pretreated and control groups. This is in accordance with our thyroid RAIU measurements after radioiodine therapy, which showed no significant difference in effective half-times of ^{131}I in the thyroid between rhTSH-pretreated patients and control patients.

During the first days after radioiodine therapy, the amount of $PB^{131}I$ was still low and the total ^{131}I activity in serum was determined predominantly by the amount of inorganic ^{131}I in the serum. During these first days, we measured much higher total ^{131}I activities in the control groups than in the rhTSH-pretreated groups. The difference at 24 h after radioiodine therapy exceeded by far the difference in therapeutic dose of radioiodine between rhTSH-pretreated groups and control groups, because the higher uptake of inorganic ^{131}I by the thyroid in the pretreated groups increased the removal rate of radioiodine from the circulation into the thyroid, whereas the removal rate to the urinary compartment was the same in both pretreated and control groups. This finding is in accordance with the iodine biokinetic model of Robertson and Gorman (14).

Conclusion

After pretreatment with a single, low dose of rhTSH, radioiodine therapy - of a dose reduced in accord with the rhTSH-induced increase in 24-h RAIU - caused lower radiation-absorbed doses in extrathyroidal organs and tissues, especially in the bladder and stomach, of patients with nodular goiter. No significant increase in the release of ^{131}I-labeled thyroid hormones from the thyroid into the circulation was observed after radioiodine therapy in rhTSH-pretreated patients. Thus, this mode of therapy can be recommended, especially when the dose of radioiodine to be administered without rhTSH pretreatment is high.

References

1 **Hegedüs L, Hansen BM, Knudsen N, Hansen JM** 1988 Reduction of size of thyroid with radioactive iodine in multinodular non-toxic goitre. Br Med J 297:661-662

2 **Nygaard B, Hegedüs L, Gervil M, Hjalgrim H, Soe-Jensen P, Hansen JM** 1993 Radioiodine treatment of multinodular non-toxic goitre. Br Med J 307:828-832

3 **Huysmans DAKC, Hermus ARMM, Corstens FHM, Barentsz JO, Kloppenborg PWC** 1994 Large, compressive goiters treated with radioiodine. Ann Intern Med 121:757-762

4 **Wesche MF, Tiel-v Buul MM, Smits NJ, Wiersinga WM** 1995 Reduction in goiter size by ^{131}I therapy in patients with non-toxic multinodular goiter. Eur J Endocrinol 132:86-87

5 **de Klerk JMH, van Isselt JW, van Dijk A, et al.** 1997 Iodine-131 therapy in sporadic nontoxic goiter. J Nucl Med 38:372-376

6 **Bonnema SJ, Bertelsen H, Mortensen J, et al.** 1999 The feasibility of high dose iodine 131 treatment as an alternative to surgery in patients with a very large goiter: effect on thyroid function and size and pulmonary function. J Clin Endocrinol Metab 84:3636-3641

7 **Wesche MFT, Tiel-v Buul MMC, Lips P, Smits NJ, Wiersinga WM** 2001 A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. J Clin Endocrinol Metab 86:998-1005

8 **Huysmans D, Hermus A, Edelbroek M, Barentz J, Corstens F, Kloppenborg P** 1997 Radioiodine for nontoxic multinodular goiter. Thyroid 7:235-239

9 **Hermus AR, Huysmans DA** 1998 Treatment of benign nodular thyroid disease. N Engl J Med 338:1438-1447

10 **Huysmans DAKC, Buijs WCAM, van de Ven MTP, et al.** 1996 Dosimetry and risk estimates of radioiodine therapy for large, multinodular goiters. J Nucl Med 37:2072-2079

11 **Huysmans DA, Nieuwlaat W-A, Erdtsieck RJ, et al.** 2000 Administration of a single low dose of recombinant human thyrotropin significantly enhances thyroid radioiodide uptake in nontoxic nodular goiter. J Clin Endocrinol Metab 85:3592-3596

12 **Nieuwlaat W-A, Hermus AR, Sivro-Prndelj F, Corstens FH, Huysmans DA** 2001 Pretreatment with recombinant human thyrotropin changes the regional distribution of radioiodine on thyroid scintigrams of nodular goiters. J Clin Endocrinol Metab 86:5330-5336

13 **Nieuwlaat W-A, Huysmans DA, van den Bosch HC, et al.** 2003 Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. J Clin Endocrinol Metab 88:3121-3129

14 **Robertson JS, Gorman CA** 1976 Gonadal radiation dose and its genetic significance in radioiodine therapy in hyperthyroidism. J Nucl Med 17:826-835

15 **DeGroot LJ** 1975 Graves' disease diagnosis and treatment: multinodular goitre. In: DeGroot LJ, Stanbury JB, eds. The Thyroid and Its Diseases. 4th ed. New York, NY: Wiley 314-367, 637-665

16 **Doering P, Kramer K** 1958 The determination of thyroid weight with scintigraphy after administration of radioiodine: a contribution to radionuclide dosing [in German]. Strahlenther 105:245-259

17 **Keating FR, Power MH, Berkson J, et al.** 1947 The urinary excretion of radioiodine in various thyroid states. J Clin Invest 26:1138-1151

18 **Loevinger R, Berman M** 1968 A schema for absorbed-dose dose calculation for biologically distributed radionuclides. Medical Internal Radiation Dose Committee (MIRD) Pamphlet No. 1. J Nucl Med 9(suppl 1):7-14

19 1990 Recommendations of the International Commission on Radiological Protection. Oxford, U.K.: Pergamon Press; 1991. ICRP Publication 60

20 **Holm LE, Hall P, Wiklund K, et al.** 1991 Cancer risk after iodine-131 therapy for hyperthyroidism. J Natl Cancer Inst 83:1072-1077

21 **Hall P, Berg G, Bjelkengren G, et al.** 1992 Cancer mortality after iodine-131 therapy for hyperthyroidism. Int J Cancer 50:886-890

22 **Hoffman DA, McConahey WM, Fraumeni JF, Kurland LT** 1982 Cancer incidence following treatment of hyperthyroidism. Int J Epidemiol 11:218-224

23 **Hoffman DA, McConahey WM** 1983 Breast cancer following iodine-131 therapy for hyperthyroidism. J Natl Cancer Inst 70:63-67

24 **Goldman MB, Maloof F, Monson RR, et al.** 1988 Radioactive iodine therapy and breast cancer: follow-up study of hyperthyroid women. Am J Epidemiol 127:969-980

25 **Taurog AM** 2000 Hormone synthesis: thyroid iodine metabolism. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid. 8th ed. Philadelphia, PA: Lippincott, Williams & Wilkins 61-85

26 **Hennemann G** 2003 Report of the 74th annual meeting of the American Thyroid Association. Thyroid International 1:8

chapter

6

6.1

Summary

6.1

Summary

In this thesis the use of recombinant human thyrotropin (rhTSH) as a possible adjunct to radioiodine therapy for thyroid volume reduction in patients with nontoxic, nodular goiter is explored.

In **chapter 1** the clinical manifestations, the diagnostic evaluation and the current treatment options (thyroidectomy, L-thyroxine treatment, and radioiodine therapy) for patients with nontoxic, nodular goiter are discussed. Thyroidectomy leads to rapid decompression of vital structures and provides tissue for pathologic examination. The efficacy of L-thyroxine treatment in patients with nontoxic, nodular goiter is, at best, modest and lifelong L-thyroxine treatment may cause bone loss and cardiac adverse effects. Radioiodine treatment is effective in more than 90% of patients with nontoxic, nodular goiter and results in a mean thyroid volume reduction of 40% after 1 year and of 50% to 60% after 3 to 5 years. In most patients compressive symptoms improve. Early side effects (radiation thyroiditis and esophagitis) are usually mild and transient. Exacerbation of compressive symptoms after radioiodine administration is rare. The development of autoimmune hyperthyroidism is the most important late complication, occurring several months after radioiodine therapy in approximately 5% of patients. The incidence of posttreatment hypothyroidism is 20% to 50% at 5 years. For each individual patient the estimated risks of both surgery and radioiodine therapy should be weighed carefully. At the moment surgery is preferred for younger patients, especially when the amount of radioiodine to be administered is high. However, for elderly patients, especially those with cardiopulmonary disease, the profits of radioiodine treatment will outweigh the lifetime risk for this mode of therapy.

Next the current knowledge on thyrotropin (TSH) is reviewed, followed by a discussion of studies using TSH extracted from bovine pituitary glands to augment radioiodine uptake in thyroid cancer patients. Because of the occurrence of allergic reactions and the relative ineffectiveness with multiple dosing due to the development of anti-TSH antibodies, bovine TSH has been abandoned for use in humans and is no longer available. Therefore thyroid hormone withdrawal leading to high endogenous serum TSH levels became the method of choice to stimulate radioiodine uptake in thyroid cancer patients.

Work from the laboratory of Weintraub in the late 1980s provided the primary sequence of the β-subunit of human TSH (hTSH). The human pituitary α-glycoprotein subunit and the human TSH β-subunit were coexpressed in Chinese hamster ovary cells resulting in the production of recombinant human TSH (rhTSH). The process of rhTSH production was modified and scaled up with assistance of scientists at Genzyme (Framingham MA, USA). RhTSH is now available as Thyrogen® (thyrotropin alfa for injection, Genzyme; Cambridge MA, USA).

Next, the in vitro en vivo studies (in animals and humans) with rhTSH are reviewed as well as the literature on the use of rhTSH in patients with differentiated thyroid cancer.

Chapter 2 to 5 contain our original studies on the use of rhTSH in patients with nontoxic, nodular goiter. In **chapter 2** we investigated whether pretreatment with a single, low dose of rhTSH enhances radioactive iodine uptake (RAIU) in 15 patients with nontoxic, nodular goiter (14 women and 1 man; aged 61 ± 11 yr). Four patients were studied twice, and 1 patient was studied 3 times. RAIU was measured both under basal conditions and after pretreatment (im) with rhTSH, given either 2 h (0.01 mg; n = 7) or 24 h [0.01 mg (n = 7) or 0.03 mg (n = 7)] before ^{131}I administration (20–40 µCi). Serum levels of TSH, free T_4 (FT_4), and total T_3 were measured at 2, 5, 8, 24, 48, 72, 96, and 192 h after rhTSH administration.

After administration of 0.01 mg rhTSH, serum TSH rose from 0.7 ± 0.5 to a peak level of 4.4 ± 1.1 mU/L ($P < 0.0001$), FT_4 rose from 16.0 ± 2.6 to 18.5 ± 3.7 pmol/L ($P < 0.0001$), and T_3 rose from 2.10 ± 0.41 to 2.63 ± 0.66 nmol/L ($P < 0.0001$). After administration of 0.03 mg rhTSH, TSH rose from 0.6 ± 0.4 to 15.8 ± 2.3 mU/L ($P < 0.0001$), FT_4 rose from 15.2 ± 1.5 to 21.7 ± 2.9 pmol/L ($P < 0.0001$), and T_3 rose from 1.90 ± 0.43 to 3.19 ± 0.61 nmol/L ($P < 0.0001$). Peak TSH levels were reached at 5–8 h and peak FT_4 and T_3 levels at 8–96 h after rhTSH administration.

Administration of 0.01 mg rhTSH 2 h before ^{131}I increased 24-h RAIU from 30 ± 11% to 42 ± 10% ($P < 0.02$), 0.01 mg rhTSH administered 24 h before ^{131}I increased 24-h RAIU from 29 ± 10% to 51 ± 10% ($P < 0.0001$), and 0.03 mg rhTSH administered 24 h before ^{131}I increased 24-h RAIU from 33 ± 11% to 63 ± 9% ($P < 0.0001$). After administration of 0.01 mg rhTSH 2 h before ^{131}I, 24-h RAIU did not increase in 1 patient, whereas the increase in 24-h RAIU was less than 10% in 2 other patients. In contrast, administration of rhTSH 24 h before ^{131}I increased 24-h RAIU by more than 10% in all 14 patients (by >20% in 10 and by >30% in 6).

We concluded that pretreatment with a single, low dose of rhTSH in patients with nontoxic, nodular goiter increased RAIU considerably. These observations hold promise that administration of rhTSH before ^{131}I therapy for nontoxic, nodular goiter would allow treatment with lower doses of ^{131}I in these patients.

The purpose of the study described in **chapter 3** was to investigate whether rhTSH pretreatment induces changes in the regional distribution of radioiodine as visualized on thyroid scintigrams in patients with nontoxic, nodular goiter.

Anterior planar thyroid ^{123}I scintigrams were obtained in 26 patients with a nodular goiter (23 women and 3 men; age, 62 ± 9 yr, mean ± SD; thyroid weight, 165 ± 72 g) 24 h after administration of a diagnostic dose of radioiodine. All patients were studied twice: first, without rhTSH pretreatment (baseline study), and second, after an im injection of 0.01 mg (n = 10) or 0.03 mg rhTSH (n = 16), given 24 h before radioiodine administration (rhTSH study). For quantification of regional differences in radioiodine uptake, a region of interest method was used.

Upon visual inspection, baseline scintigrams showed a heterogeneous uptake of radioiodine. In general, rhTSH scintigrams also showed heterogeneous radioiodine uptake. In some patients, the distribution of radioiodine in the rhTSH scintigram was considerably more homogeneous than in the baseline scintigram. In a few patients, originally "cold" areas had changed into "hot" ones, whereas originally hot areas had changed into cold ones. Quantification of regional radioiodine uptake showed that pretreatment with rhTSH caused a larger increase in radioiodine uptake in relatively cold areas and a smaller increase in radioiodine uptake in relatively hot areas, compared with the increase in radioiodine uptake in the entire thyroid. In patients with a baseline serum TSH level of 0.5 mU/L or lower, the increase in radioiodine uptake in relatively cold areas was significantly larger than in patients with a baseline serum TSH level higher than 0.5 mU/L.

We concluded that a single, low dose of rhTSH caused a more homogeneous distribution of radioiodine within the thyroid gland in patients with a nodular goiter by stimulating radioiodine uptake in relatively cold areas more than in relatively hot areas. This was most marked in patients with a low baseline serum TSH level. Our data suggest that pretreatment with rhTSH may improve the efficacy of radioiodine treatment for volume reduction of nodular goiters, especially in patients with a low baseline serum TSH level.

In **chapter 4** we studied the safety and efficacy of therapy with a reduced dose of ^{131}I after pretreatment with rhTSH. Twenty-two patients with nodular goiter received ^{131}I therapy 24 h after intramuscular administration of 0.01 (n = 12) or 0.03 (n = 10) mg rhTSH. In preceding diagnostic studies using tracer doses of ^{131}I, 24-h RAIU without and with rhTSH pretreatment (either 0.01 or 0.03 mg) were compared. Therapeutic doses of ^{131}I were adjusted to the rhTSH-induced increases in 24-h RAIU and were aimed at 100 μCi/g thyroid tissue retained at 24 h. Pretreatment with rhTSH allowed dose reduction of ^{131}I therapy by a factor of 1.9 ± 0.5 in the 0.01 mg and by a factor of 2.4 ± 0.4 in the 0.03 mg rhTSH group ($P < 0.05$, 0.01 vs 0.03 mg rhTSH). Before and 1 year after therapy thyroid volume and the smallest cross-sectional area of the tracheal lumen (SCAT) were measured with MRI. During the year of follow-up, serum TSH, FT_4, T_3 and TSH receptor antibodies (TRAb) were measured at regular intervals.

Thyroid volume before therapy was 143 ± 54 mL in the 0.01 mg and 103 ± 44 mL in the 0.03 mg rhTSH group. One year after treatment thyroid volume reduction was 35 ± 14% (0.01 mg rhTSH) and 41 ± 12% (0.03 mg rhTSH). In both groups SCAT increased significantly. In the 0.01 mg rhTSH group, serum FT_4 rose after ^{131}I treatment from 15.8 ± 2.8 to 23.2 ± 4.4 pmol/L. In the 0.03 mg rhTSH group, serum FT_4 rose from 15.5 ± 2.5 to 23.5 ± 5.1 pmol/L. Individual peak FT_4 levels, reached between 1 and 28 days after ^{131}I treatment, were above the normal range in 12 patients. TRAbs were negative in all patients before therapy and became positive in 4 patients. Hyperthyroidism developed in 3 of these 4 patients between 23 and 25 weeks after therapy. We concluded that in patients with nodular goiter pretreatment with a single, low dose of rhTSH allowed approximately 50% to 60% reduction of the therapeutic dose of radioiodine without compromising the efficacy of thyroid volume reduction.

In **chapter 5** dosimetric aspects of therapy with a reduced dose of ^{131}I after pretreatment with rhTSH in patients with nontoxic, nodular goiter were investigated. In this study 36 patients were treated with ^{131}I to reduce thyroid volume. Nine patients were pretreated with a single dose of 0.01 mg rhTSH, and 9 patients with 0.03 mg rhTSH. There were 2 control groups of 9 patients, matched for thyroid weight and 24-h RAIU, who were not pretreated with rhTSH. The therapeutic dose of ^{131}I was aimed at delivering 3.7 MBq of ^{131}I/g of thyroid tissue retained at 24 h. Thyroid radioactivity measurements after the administration of ^{131}I were performed every 24 hours for 3 days, and on days 7, 10, 14, 21, and 28. A model of iodine biokinetics was used to estimate absorbed doses in organs. Protein-bound ^{131}I activity was measured at 1, 2, 3, 7, and 10 days and at 2, 3, and 4 weeks after ^{131}I therapy.

The administered activities were 1.5 times lower in the 0.01 mg rhTSH group and 1.9 times lower in the 0.03 mg rhTSH group compared to those in the control groups. The absorbed dose in the thyroid was similar in the rhTSH-pretreated groups and in the control groups. In the organs of excretion (bladder) and uptake (stomach) of inorganic iodide the absorbed doses were 2- to 3-fold lower in the pretreated groups than in the control groups. The effective dose equivalent outside the thyroid was considerably lower in the rhTSH-pretreated groups than in their respective control groups (1.6 fold in the 0.01 mg rhTSH group and 2.3 fold in the 0.03 mg rhTSH group). The time course of protein-bound ^{131}I activity in serum and the cumulated protein-bound ^{131}I activity in serum did not differ significantly between rhTSH-pretreated and control groups.

From this study it can be concluded that ^{131}I therapy after pretreatment with a single, low dose of rhTSH, with a dose reduced according to the rhTSH-induced increase in 24-h RAIU, caused lower radiation-absorbed doses in extrathyroidal organs and tissues, especially bladder and stomach, and no significant increase in the release of ^{131}I-labeled thyroid hormones from the thyroid into the circulation in patients with nodular goiter. Thus, this mode of therapy can be recommended, especially when the dose of radioiodine to be administered without rhTSH pretreatment is high.

6.2

Perspective

Dyde A. Huysmans, Willy-Anne Nieuwlaat,
and Ad R. Hermus

Department of Nuclear Medicine (D.A.H., W.-A.N.),
Catharina Hospital, Eindhoven;
Department of Endocrinology (W.-A.N., A.R.H.),
Radboud University Nijmegen Medical Center, Nijmegen,
The Netherlands

Published in part as
Towards Larger Volume Reduction of Nodular Goitres by Radioiodine Therapy: a Role for Pretreatment with Recombinant Human Thyrotropin?
Clinical Endocrinology 2004; 60(3):297-299

6.2

Perspective

Towards larger volume reduction of nodular goiters by ^{131}I: a role for pretreatment with recombinant human TSH?

A drawback of radioiodine therapy for nodular goiter (with ^{131}I doses aimed at approximately 100–150 μCi retained per gram of thyroid tissue at 24 h) is that mean thyroid volume reduction is not greater than approximately 40% after 1 year, and not all patients respond. Preliminary data by Le Moli et al. (1) suggest that goiter reduction might be augmented by increasing the radiation-absorbed dose in the thyroid. Such an increase can be achieved by simply enlarging the administered dose of radioiodine, but this will further increase the radiation burden to extrathyroidal organs. Alternatively, it should be possible to increase the radiation-absorbed dose in the thyroid without increasing the administered dose of radioiodine, by stimulating thyroid radioiodine uptake by pretreatment with recombinant human TSH (rhTSH).

A first study on this issue has recently been published (2). Thirty-four patients with large, multinodular goiters (80–728 mL), of whom 22 were subclinically hyperthyroid and 7 overtly hyperthyroid, were randomized in two groups. Patients of group 1 (n = 17) were treated with radioiodine only, using a quite rough dosing regimen (30–50 mCi for goiters <140 g, 58–80 mCi for goiters 150–190 g, and 150 mCi for goiters 200-728 g). Patients of group 2 (n = 17) received comparable doses of radioiodine 24 h after pretreatment with 0.45 mg rhTSH. This rhTSH dose is higher than used in our studies. Thyroid volume measurements before and 6 and 12 months after therapy were done with CT.

The administered doses of radioiodine were 73 ± 12 μCi/g retained at 24 h in the control patients and 191 ± 75 μCi/g in the patients pretreated with rhTSH. High peak levels of FT_4 were reached in group 2 (59 ± 22 pmol/L, compared with 24 ± 7 pmol/L in group 1). Not surprisingly, symptoms of thyroiditis (pain in the thyroid region in 52% of patients of group 2, compared to 23% of patients in group 1) and esophagitis (17% versus 11%) were more frequent in the pretreated patients. Surprisingly, no symptoms of hyperthyroidism or worsening of heart diseases were observed.

Interestingly, 1 year after therapy thyroid volume reduction was 58% ± 13% in group 2 patients in comparison with 40% ± 12% in group 1 patients ($P < 0.05$). The obtained volume reduction after rhTSH administration was considerably more than in previous studies using radioiodine in doses of 100-150 μCi/g without rhTSH pretreatment.

We published in the March 2004 issue of Clinical Endocrinology the following commentary (3) on the study by Silva et al.:

"

In the last two decades it has been demonstrated that radioiodine (^{131}I) is an effective therapy for thyroid volume reduction in patients with toxic and non-toxic nodular goiter. In these patients, ^{131}I treatment leads to a significant decrease in goiter size. In most patients compressive symptoms improve as well. The decrease in compressive symptoms is accompanied by significant tracheal widening and improvement of respiratory function (4).

^{131}I treatment is especially attractive in elderly patients who have a high operative risk and in those who refuse surgery. However, in patients with nontoxic, nodular goiter thyroid radioactive iodide uptake (RAIU) is usually rather low, especially in areas with a high iodine intake. As a result, high doses of ^{131}I are often needed for thyroid volume reduction, causing a relatively high radiation burden to extrathyroidal organs (5). Therefore, it is of interest to explore strategies to enhance RAIU in these patients.

In the last decade rhTSH has become available for diagnostic use in patients with differentiated thyroid cancer. It has been shown that rhTSH stimulates RAIU in thyroid remnants and thyroid cancer tissue (6,7). Recently, we reported that rhTSH stimulates RAIU also in patients with nodular goiter: the administration of a single, low dose of 0.01 or 0.03 mg rhTSH doubled 24-h RAIU in these patients (8). Pretreatment with rhTSH also caused a more homogeneous distribution of radioiodine on the thyroid scintigrams of nodular goiters by stimulating radioiodine uptake in relatively cold areas more than in relatively hot areas, especially in patients with a low baseline serum TSH level (9). These observations suggest that administration of rhTSH before ^{131}I therapy for volume reduction of nodular goiter may allow treatment with lower doses of ^{131}I without diminishing the radiation-absorbed dose in the thyroid and the efficacy of this mode of therapy. Indeed, pretreatment with a single, low dose of 0.01 or 0.03 mg rhTSH allowed approximately 50-60% reduction of the therapeutic dose of radioiodine without compromising the efficacy of thyroid volume reduction (10). As the radiation burden of radioiodine therapy to extrathyroidal organs is directly related to the administered ^{131}I dose (5), such a dose reduction may render radioiodine therapy more attractive for younger patients and may allow for more patients to be treated on an out-patient basis.

A major drawback of radioiodine therapy for nodular goiter (with ^{131}I doses aimed at approximately 100-150 µCi retained per gram of thyroid tissue at 24 h) is that mean thyroid volume reduction is not greater than approximately 40% after 1 year, and 50-60% after 3-5 years (4). Moreover, not all patients respond. Preliminary data by Le Moli et al. (1) suggest that goiter reduction can be augmented by increasing the radiation-absorbed dose in the thyroid. Such an increase can be achieved by simply enlarging the administered dose of radioiodine, but this will further increase the radiation burden to extrathyroidal organs. Alternatively, it should be possible to increase the radiation-absorbed dose in the thyroid without increasing the administered dose of radioiodine, by stimulating RAIU using pretreatment with rhTSH.

Silva et al. (2) report 34 patients with large, nodular goitres (22 were subclinically hyperthyroid and 7 overt hyperthyroid) who were randomized to radioiodine therapy alone or to radioiodine therapy in comparable doses but with pretreatment with a relatively high dose of rhTSH (0.45 mg), given 24 h before radioiodine administration. Patients pretreated with rhTSH had a significantly larger thyroid volume reduction after 1 year (58 ± 13%) than patients given radioiodine without rhTSH pretreatment (40 ± 12%).

From data provided in tables 1 and 2 of their report, we calculated the dose retained in the thyroid at 24 h for individual patients in both groups. This parameter was considerably higher in the rhTSH-pretreated patients (191 ± 75 µCi per gram of thyroid tissue) than in the patients not pretreated with rhTSH (73 ± 22 µCi/g). It seems likely that the higher thyroid volume reduction in the rhTSH-pretreated group can be explained by the higher retention of radioiodine in the thyroid. An alternative explanation is that pretreatment with rhTSH improves thyroid volume reduction by causing a more homogeneous distribution of radioiodine within the thyroid, especially increasing the uptake of radioiodine in relatively cold areas (9).

It may be anticipated that a higher dose of radioiodine retained in the thyroid will be accompanied by more severe early adverse effects due to radiation-induced thyroiditis and esophagitis. Indeed, in comparison with patients not pretreated with rhTSH, rhTSH-pretreated patients had a higher incidence of pain in the thyroid region (52% versus 23%), complaints due to esophagitis (17% versus 11%), and weight loss (65% versus 52%).

Another consequence of thyroiditis is acute enlargement of the thyroid gland with (further) compression of the trachea. For radioiodine doses aimed at approximately 100-150 µCi retained per gram of thyroid tissue at 24 h, increases in thyroid volume 1 week after radioiodine therapy up to 25% have been found (9,11,12). Silva et al. did not quantify thyroid volume changes in the first period after radioiodine therapy. Therefore, it remains to be investigated whether the larger ^{131}I doses retained in the thyroid as used by Silva et al. cause larger increases in thyroid volume in the first period after radioiodine treatment.

Mild increases in serum thyroid hormone levels due to radiation-induced thyroiditis are commonly seen in the first weeks after radioiodine treatment of nodular goitre, with maximum levels reached at approximately 2 weeks after therapy (11). It has also been demonstrated that administration of low doses of rhTSH (0.01 or 0.03 mg) in patients with nodular goiter results in mild increases in serum thyroid hormone levels, with maximum levels reached at 1 to 4 days after administration of rhTSH (8). It may be anticipated that pretreatment with a relatively high dose of rhTSH followed by a full dose of radioiodine, leading to a high radiation-absorbed dose in the thyroid, will result in larger increases in serum thyroid hormone levels. Indeed, peak FT_4 levels reached in the rhTSH-pretreated patients studied by Silva et al. were much higher than those in the patients treated with radioiodine alone (59 ± 22 versus 24 ± 7 pmol/L), despite a low-iodine diet in all patients and methimazole pretreatment in the 7 overtly hyperthyroid patients. The highest FT_4 levels were reached already at 1 to 3 days after radioiodine therapy, suggesting that rhTSH administration was the most important cause of the rise. Fortunately, no hyperthyroid symptoms or worsening of heart diseases were observed. The authors give 3 possible explanations: the rise in thyroid hormone levels was of short duration, most patients had cardiac medications, and all patients were confined to their beds for 5 to 9 days after radioiodine therapy.

A late adverse effect of radioiodine treatment of nodular goiter is development of hypothyroidism. Probably related to the higher radioiodine dose retained in the thyroid, Silva et al. found that hypothyroidism 1 year after radioiodine therapy was more frequent in the rhTSH-pretreated patients than in the patients not pretreated with rhTSH (65% versus 21%).

The study of Silva et al. is the first to show that the efficacy of radioiodine therapy of nodular goiters can be improved by pretreatment with rhTSH. However, conclusions are based on small numbers of patients and both toxic (4 of them had used amiodarone) and nontoxic patients were included. Moreover, no attempt was made to calculate precisely the radioiodine doses to be administered (radioiodine doses were based on a rather simple algorithm with estimated thyroid volume as the only parameter).

Before rhTSH can be advised as an adjunct to improve the efficacy of radioiodine therapy in nodular goiter, further studies are needed. First, it has to be determined in a formal dose-response study which dose of rhTSH is optimal for this purpose. Such a dose should stimulate RAIU considerably, but should not cause unacceptable rises in serum thyroid hormone levels. Then, radioiodine therapy with and without pretreatment with that particular dose of rhTSH should be investigated in randomized studies. Such studies should look carefully at dose-response relationships with respect to efficacy and adverse effects. Given the heterogeneity of nodular goiters, large groups of patients will be needed. ”

Recently, two studies were presented showing results of treatment of patients with nontoxic, nodular goiter with an ambulatory dose of 30 mCi ^{131}I after prestimulation with rhTSH. Duick and Baskin (13) prepared 6 patients with 0.3 mg rhTSH 72 hours before radioiodine therapy and 10 patients with 0.9 mg rhTSH 24 hours before radioiodine therapy. Baseline thyroid volume was 81 ± 25 mL. In the 6 patients who received 0.3 mg rhTSH, 4-h radioactive iodine uptake 72 hours after rhTSH increased 4-fold (from 4% ± 1% to 17% ± 8%). Estimated gland size reduction was 30–40% after 3–7 months in 15 of 16 patients.

Graf and co-workers (14) prepared 26 patients with 2 injections of 0.1 mg rhTSH, given 48 and 24 hours before radioiodine therapy. Baseline thyroid volume was 116 ± 37 ml. 24-h uptake of a dose of radioiodine given 24 hours after the last dose of rhTSH increased 4-fold (from 12% to 54%). FT_4 levels increased to a peak level of 3.2 ± 1.1 ng/dL, 24 h after the last dose of rhTSH. Mean thyroid volume reduction, as assessed by CT, was 39% after 6 months.

However, before rhTSH can be advised as an adjunct to improve the efficacy of radioiodine therapy in nodular goiter, two key questions should be answered. First, at the moment we do not know which dose of rhTSH is optimal for this purpose. Such a dose should not cause unacceptable rises in serum thyroid hormone levels and thyroid volume, and, at the same time, it should stimulate radioiodine

uptake considerably and cause a more homogeneous distribution of radioiodine within the thyroid gland.

Carefully determining the safety of administering rhTSH to patients with nodular goiter should indeed be a key issue, as injection of rhTSH causes increases in serum thyroid hormone levels and thyroid volume in subjects with functioning thyroid tissue. For example, in a recent study (15) administration of 0.9 mg rhTSH to healthy subjects more than doubled serum FT_4 levels and increased thyroid volume by 35%. Maximal effects were reached 48 hours after rhTSH administration.

The second question to be answered is: which thyroid radiation dose (in µCi per gram of thyroid tissue) is optimal, both in terms of safety (minimal short-term radioiodine-induced increases in serum thyroid hormone levels and in thyroid volume) and in terms of efficacy (long-term thyroid volume reduction).

As mentioned above, hardly any data are available which address the hypothesis that increasing the thyroid radiation dose to levels above 100-150 µCi/g of thyroid tissue, whether or not after prestimulation with rhTSH, improves the efficacy of radioiodine therapy of nodular goiters.

We conclude that more data are needed, before rhTSH can be advised as an adjunct to improve the efficacy of radioiodine therapy in nodular goiter. Aims of such phase II and III studies should be to find evidence and definitive proof that increasing the radiation-absorbed dose in the thyroid by pretreatment with rhTSH is safe and results in a greater reduction in thyroid volume. Such studies may use a fixed dose (for example 15 or 30 mCi) or a calculated dose of radioiodine.

References

1 **Le Moli R, Wesche MFT, Tiel-van Buul MMC, Wiersinga WM** 1999 Determinants of longterm outcome of radioiodine therapy of sporadic non-toxic goitre. Clin Endocrinol (Oxf) 50:783-789

2 **Silva MN, Rubio IG, Romao R, Gebrin EM, Buchpiguel C, Tomimori E, Camargo R, Cardia MS, Medeiros-Neto G** 2004 Administration of a single dose of recombinant human thyrotrophin enhances the efficacy of radioiodine treatment of large compressive multinodular goitres. Clin Endocrinol (Oxf) 60:300-308

3 **Huysmans DA, Nieuwlaat W-A, Hermus AR** 2004 Towards larger volume reduction of nodular goitres by radioiodine therapy: a role for pretreatment with recombinant human thyrotropin? Clin Endocrinol (Oxf) 60:297-299

4 **Hegedüs L, Bonnema SJ, Bennedbæk FN** 2003 Management of simple nodular goiter: current status and future perspectives. Endocr Rev 24:102-132

5 **Huysmans DAKC, Buijs WCAM, van de Ven MTP, van den Broek WJM, Kloppenborg PWC, Hermus ARMM, Corstens FHM** 1996 Dosimetry and risk estimates of radioiodine therapy for large, multinodular goiters. J Nucl Med 37:2072-2079

6 **Ladenson PW, Braverman LE, Mazzaferri EL, Brucker-Davis F, Cooper DS, Garber JR, Wondisford FE, Davies TF, DeGroot LJ, Daniels GH, Ross DS, Weintraub BD** 1997 Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N Engl J Med 337:888-896

7 **Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, Cooper DS, Graham KE, Braverman LE, Skarulis MC, Davies TF, DeGroot LJ, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Becker DV, Maxon HR, III, Cavalieri RR, Spencer CA, McEllin K, Weintraub BD, Ridgway EC** 1999 A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J Clin Endocrinol Metab 84:3877-3885

8 **Huysmans DA, Nieuwlaat W-A, Erdtsieck RJ, Schellekens AP, Bus JW, Bravenboer B, Hermus AR** 2000 Administration of a single low dose of recombinant human thyrotropin significantly enhances thyroid radioiodide uptake in nontoxic nodular goiter. J Clin Endocrinol Metab 85:3592-3596

9 **Nieuwlaat W-A, Hermus AR, Sivro-Prndelj F, Corstens FH, Huysmans DA** 2001 Pretreatment with recombinant human TSH changes the regional distribution of radioiodine on thyroid scintigrams of nodular goiters. J Clin Endocrinol Metab 86:5330-5336

10 **Nieuwlaat W-A, Huysmans DA, van den Bosch HC, Sweep CG, Ross HA, Corstens FH, Hermus AR** 2003 Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. J Clin Endocrinol Metab 88:3121-3129

11 **Nygaard B, Faber J, Hegedüs L** 1994 Acute changes in thyroid volume and function following 131I therapy of multinodular goitre. Clin Endocrinol (Oxf) 41:715-718

12 **Bonnema SJ, Bertelsen H, Mortensen J, Andersen PB, Knudsen DU, Bastholt L, Hegedüs L** 1999 The feasibility of high dose iodine 131 treatment as an alternative to surgery in patients with a very large goiter: effect on thyroid function and size and pulmonary function. J Clin Endocrinol Metab 84:3636-3641

13 **Duick DS, Baskin HJ** 2003 Utility of recombinant human thyrotropin for augmentation of radioiodine uptake and treatment of nontoxic and toxic multinodular goiters. Endocr Pract 9:204-209

14 **Graf H, Mesa CO, Albino CC** 2003 Radioactive Iodine (^{131}I) in Multinodular Goiter (MNG) Treatment with the Aid of Recombinant Human TSH (rhTSH, Thyrogen®). Program Number 174, Annual 75th Meeting of the American Thyroid Association 2003, Palm Beach, FL, September 16-21:726

15 **Nielsen VE, Bonnema SJ, Hegedüs L** 2004 Effects of 0.9 mg recombinant human thyrotropin on thyroid size and function in normal subjects: a randomized, double-blind, cross-over trial. J Clin Endocrinol Metab 89:2242-2247

chapter

7

7.1

Samenvatting

7.1

Samenvatting

In deze dissertatie wordt het gebruik van recombinant humaan thyrotropine (rhTSH) onderzocht als een mogelijk adjuvans bij therapie met radioactief jodium bedoeld om het schildkliervolume bij patiënten met een niet-toxisch, nodulair struma te reduceren.

In **hoofdstuk 1** worden de klinische presentatie, de diagnostiek en de huidige behandelopties (chirurgie, behandeling met L-thyroxine en therapie met radioactief jodium) bij patiënten met een niet-toxisch, nodulair struma bediscussieerd. Thyreoïdectomie geeft een snelle decompressie van vitale structuren en verschaft weefsel voor pathologisch-anatomisch onderzoek. De effectiviteit van behandeling met L-thyroxine bij patiënten met een niet-toxisch, nodulair struma is hooguit matig en levenslange behandeling met L-thyroxine kan botverlies en cardiale complicaties veroorzaken. Behandeling met radioactief jodium is effectief bij meer dan 90% van de patiënten met een niet-toxisch, nodulair struma en resulteert in een gemiddelde afname van het schildkliervolume met 40% na 1 jaar en 50 tot 60% na 3 tot 5 jaar. Bij de meeste patiënten verminderen de symptomen ten gevolge van compressie van vitale structuren in de hals. Vroege bijwerkingen (bestralingsthyreoïditis en -oesofagitis) zijn gewoonlijk gering en van voorbijgaande aard. Verergering van compressiesymptomen na de toediening van radioactief jodium is zeldzaam. De belangrijkste late complicatie is het ontstaan van een auto-immuun hyperthyreoïdie. Hetgeen optreedt bij ongeveer 5% van de patiënten enkele maanden na de behandeling met radioactief jodium. De prevalentie van hypothyreoïdie na de behandeling bedraagt 20 tot 50% na 5 jaar. Voor iedere individuele patiënt dienen de risico's van chirurgie en therapie met radioactief jodium zorgvuldig tegen elkaar te worden afgewogen. Op dit moment verdient chirurgie de voorkeur bij jongere patiënten, met name wanneer de toe te dienen dosering radioactief jodium hoog is. Echter bij oudere patiënten, in het bijzonder degenen met een cardiopulmonale aandoening, zullen de voordelen van de behandeling met radioactief jodium tegen het mogelijk risico op lange termijn van deze behandeling opwegen.

Vervolgens wordt een overzicht gegeven van de huidige kennis van thyrotropine (TSH), gevolgd door een bespreking van de studies waarin TSH, verkregen uit de hypofyses van runderen, wordt gebruikt om de opname van radioactief jodium te verhogen bij patiënten met schildklierkanker. Aangezien er allergische reacties optraden en er na meerdere doseringen relatieve ineffectiviteit ontstond ten gevolge van het ontwikkelen van anti-TSH antilichamen, is het gebruik van runder-TSH bij mensen verlaten. Mede daardoor is het onttrekken van behandeling met schildklierhormoon, hetgeen tot hoge endogene serum spiegels van TSH leidt, de methode van eerste keus geworden om de opname van radioactief jodium bij schildklierkankerpatiënten te stimuleren.

Werk in het laboratorium van Weintraub gedurende de late jaren 80 van de vorige eeuw leverde de primaire sequentie op van de β-subunit van humaan TSH (hTSH). De humane α-glycoproteïne subunit en de humane TSH β-subunit werden tot co-expressie gebracht in ovariële cellen van de chinese hamster, hetgeen resulteerde in de productie van recombinant humaan TSH (rhTSH). Het productieproces van rhTSH werd gemodificeerd en opgeschaald met assistentie van wetenschappers van Genzyme (Framingham MA, USA). RhTSH is nu verkrijgbaar als Thyrogen® (thyrotropin alfa voor injectie, Genzyme; Cambridge MA, USA).

Vervolgens wordt een overzicht gegeven van de in vitro en in vivo studies met rhTSH (bij dieren en gezonde mensen) en tevens van de literatuur over het gebruik van rhTSH bij patiënten met een gedifferentieerd schildkliercarcinoom.

Hoofdstuk 2 tot en met 5 omvatten onze originele studies naar het gebruik van rhTSH bij patiënten met een niet-toxisch, nodulair struma. In **hoofdstuk 2** onderzochten we of voorbehandeling met één enkele, lage dosis rhTSH de opname van radioactief jodium in de schildklier (radioactive iodine uptake; RAIU) bij 15 patiënten (14 vrouwen en 1 man; leeftijd 61 ± 11 jaar) met een niet-toxisch, nodulair struma verhoogt. Vier patiënten werden tweemaal onderzocht en 1 patiënt driemaal. De RAIU werd zowel onder basale condities als na voorbehandeling (i.m.) met rhTSH gemeten. Het rhTSH werd óf 2 uur (0,01 mg; n = 7) of 24 uur [0,01 mg (n = 7) of 0,03 mg (n = 7)] voor de ^{131}I toediening (20–40 µCi) gegeven. Serumspiegels van TSH, vrij T_4 (FT_4), en totaal T_3 werden 2, 5, 8, 24, 48, 72, 96 en 192 uur na rhTSH toediening bepaald.

Na toediening van 0,01 mg rhTSH steeg het serum TSH van 0,7 ± 0,5 naar een maximale waarde van 4,4 ± 1,1 mU/L ($P < 0,0001$), FT_4 steeg van 16,0 ± 2,6 naar 18,5 ± 3,7 pmol/L ($P < 0,0001$), en T_3 steeg van 2,10 ± 0,41 naar 2,63 ± 0,66 nmol/L ($P < 0,0001$). Na toediening van 0,03 mg rhTSH steeg het serum TSH van 0,6 ± 0,4 naar 15,8 ± 2,3 mU/L ($P < 0,0001$), FT_4 steeg van 15,2 ± 1,5 naar 21,7 ± 2,9 pmol/L ($P < 0,0001$), en T_3 steeg van 1,90 ± 0,43 naar 3,19 ± 0,61 nmol/L ($P < 0,0001$). De maximale TSH-spiegels werden bereikt 5–8 uur en de maximale FT_4 en T_3 spiegels 8–96 uur na rhTSH toediening.

Injectie van 0,01 mg rhTSH 2 uur vóór de behandeling met ^{131}I deed de 24-uurs RAIU toenemen van 30 ± 11% tot 42 ± 10% ($P < 0,02$), 0,01 mg rhTSH 24 uur vóór de toediening van ^{131}I deed de 24-uurs RAIU toenemen van 29 ± 10% tot 51 ± 10% ($P < 0,0001$) en 0,03 mg rhTSH 24 uur vóór de toediening van ^{131}I deed de 24-uurs RAIU toenemen van 33 ± 11% tot 63 ± 9% ($P < 0,0001$). Na toediening van 0,01 mg rhTSH 2 uur vóór de ^{131}I nam de 24-uurs RAIU bij 1 patiënt niet toe, terwijl de toename van de 24-uurs RAIU bij 2 andere patiënten minder was dan 10%. Toediening

van rhTSH 24 uur vóór de ^{131}I deed de 24-uurs RAIU met meer dan 10% toenemen bij alle 14 patiënten (met meer dan 20% bij 10 en met meer dan 30% bij 6).

We concludeerden dat één enkele, lage dosis rhTSH bij patiënten met een niet-toxisch, nodulair struma de radioactief jodium opname aanzienlijk doet toenemen. Deze observaties suggereren dat toediening van rhTSH vóór ^{131}I therapie bij niet-toxisch, nodulair struma, behandeling met lagere doses ^{131}I bij deze patiënten mogelijk kan maken.

In de studie, die wordt beschreven in **hoofdstuk 3**, is onderzocht of voorbehandeling met rhTSH veranderingen veroorzaakt in de verdeling van radioactief jodium binnen de schildklier op schildklierscintigrammen van patiënten met niet-toxisch, nodulair struma.

Anterieure planaire schildklierscintigrammen met ^{123}I werden uitgevoerd bij 26 patiënten met een nodulair struma (23 vrouwen en 3 mannen; leeftijd 62 ± 9 jaar; schildkliergewicht, 165 ± 72 g), 24 uur na toediening van een diagnostische dosis radioactief jodium. Alle patiënten werden tweemaal bestudeerd: eerst zonder rhTSH voorbehandeling (basale studie) en daarna na een i.m. injectie met 0,01 mg (n = 10) of 0,03 mg (n = 16) rhTSH 24 uur vóór toediening van het radioactief jodium (rhTSH studie) toegediend. Ter kwantificering van de regionale verschillen in opname van radioactief jodium werd een methode met “regions of interest” gebruikt.

Bij visuele beoordeling liet de basale scintigrafie een heterogene opname van radioactief jodium zien. In het algemeen liet ook de scintigrafie na rhTSH een heterogene opname van radioactief jodium zien. Bij enkele patiënten was de verdeling van het radioactief jodium na rhTSH aanzienlijk homogener dan bij de basale scintigrafie. Bij een paar patiënten waren aanvankelijk “koude” gebieden veranderd in “warme” terwijl van origine warme gebieden waren veranderd in koude. Kwantificering van de regionale opname van radioactief jodium liet zien dat voorbehandeling met rhTSH een grotere toename van de opname van radioactief jodium in relatief koude gebieden en een kleinere toename van de opname van radioactief jodium in relatief warme gebieden veroorzaakt, vergeleken met de toename van de opname van radioactief jodium in de gehele schildklier. Bij patiënten met een basale TSH-spiegel van 0,5 mU/L of lager was de toename van de opname van radioactief jodium in relatief koude gebieden significant groter dan bij patiënten met een basale TSH-spiegel in serum hoger dan 0,5 mU/L.

We concludeerden dat één enkele, lage dosis rhTSH een meer homogene distributie van radioactief jodium in de schildklier van patiënten met een nodulair struma veroorzaakt doordat de opname van radioactief jodium in relatief koude gebieden

meer wordt gestimuleerd dan in relatief warme gebieden. Dit was het meest uitgesproken bij patiënten met een lage basale TSH-spiegel in serum. Onze data suggereren dat voorbehandeling met rhTSH de effectiviteit van behandeling met radioactief jodium ter volumereductie van nodulair struma zou kunnen verbeteren, in het bijzonder bij patiënten met een lage basale TSH-spiegel.

In **hoofdstuk 4** hebben we de veiligheid en de effectiviteit van therapie met een gereduceerde dosis ^{131}I na voorbehandeling met rhTSH bestudeerd. Vierentwintig patiënten met nodulair struma werden met ^{131}I behandeld 24 uur na intramusculaire toediening van 0,01 (n=12) of 0,03 (n=10) mg rhTSH. In voorafgaande diagnostische studies waarin tracerdoses ^{131}I werden gebruikt werden de 24-uurs RAIU zonder en met rhTSH voorbehandeling (0,01 of 0,03 mg) vergeleken. De therapeutische doses met ^{131}I werden aangepast aan de door rhTSH geïnduceerde toename van de 24-uurs RAIU. Doel was een bestralingsdosis van 100 μCi/g schildklierweefsel geretineerd na 24 uur. Voorbehandeling met rhTSH maakte reductie van de therapeutische dosis ^{131}I mogelijk met een factor van 1,9 ± 0,5 bij de 0,01 mg rhTSH groep en met een factor van 2,4 ± 0,4 bij de 0,03 mg rhTSH groep ($P < 0,05$; 0,01 vs 0,03 mg rhTSH). Vóór en 1 jaar na therapie werden het schildkliervolume en de kleinste tracheadoorsnede [smallest cross-sectional area of the tracheal lumen (SCAT)] gemeten met MRI. Gedurende het jaar van follow-up werden serumspiegels van TSH, FT_4, T_3 en TSH-receptor-antilichamen met regelmatige tussenpozen gemeten.

Het schildkliervolume vóór therapie was 143 ± 54 mL in de 0,01 mg rhTSH groep en 103 ± 44 mL in de 0,03 mg rhTSH groep. Een jaar na behandeling was het schildkliervolume afgenomen met 35 ± 14% (0,01 mg rhTSH) en 41 ± 12% (0,03 mg rhTSH). Bij beide groepen was de SCAT significant toegenomen. In de 0,01 mg rhTSH groep steeg het serum FT_4 na de ^{131}I behandeling van 15,8 ± 2,8 naar 23,2 ± 4,4 pmol/L. In de 0,03 mg rhTSH groep steeg het serum FT_4 van 15,5 ± 2,5 naar 23,5 ± 5,1 pmol/L. Individuele FT_4-piekspiegels werden bereikt tussen 1 en 28 dagen na de ^{131}I behandeling en waren hoger dan de bovengrens van normaal bij 12 patiënten. De bepaling van antistoffen tegen de TSH receptor was negatief bij alle patiënten vóór therapie en werd positief na therapie met ^{131}I bij 4 patiënten. Er ontstond een hyperthyreoïdie bij 3 van deze 4 patiënten tussen de 23 en 25 weken na therapie. We concludeerden dat bij patiënten met een nodulair struma voorbehandeling met één enkele, lage dosis rhTSH zorgt dat de therapeutische dosis radioactief jodium met 50-60% kan worden verlaagd, zonder dat de effectiviteit ten aanzien van de volumereductie wordt verminderd.

In **hoofdstuk 5** worden de dosimetrische aspecten van therapie met een gereduceerde dosis ^{131}I na voorbehandeling met rhTSH bij patiënten met een niet-toxisch, nodulair struma bestudeerd. In deze studie werden 36 patiënten behandeld met ^{131}I ter volumereductie van de schildklier. Negen patiënten werden voorbehandeld met eenmalig 0,01 mg rhTSH, en 9 patiënten met eenmalig 0,03 mg rhTSH. Er waren 2 controlegroepen van 9 patiënten, gematched op schildkliergewicht en 24-uurs RAIU, die niet werden voorbehandeld met rhTSH. De therapeutische dosis ^{131}I was gericht op een na 24 uur geretineerde dosis van 100 µCi/g schildklierweefsel. Metingen van radioactiviteit in de schildklier na de toediening van ^{131}I werden uitgevoerd na 24, 48 en 72 uur en op dag 7, 10, 14, 21 en 28. Een model voor de biokinetiek van jodium werd gebruikt om de geabsorbeerde doses in de organen te bepalen. Eiwit-gebonden ^{131}I activiteit werd gemeten 1, 2, 3, 7 en 10 dagen en 2, 3 en 4 weken na de ^{131}I therapie.

De toegediende activiteit was 1,5 maal lager in de 0,01 mg rhTSH groep en 1,9 maal lager in de 0,03 mg rhTSH groep vergeleken met die in de respectievelijke controlegroepen. De geabsorbeerde dosis in de schildklier was gelijk in de met rhTSH voorbehandelde groepen en de controlegroepen. In de blaas (waarin anorganisch jodium wordt uitgescheiden) en in de maag (waarin anorganisch jodium wordt opgenomen) waren de geabsorbeerde doses 2- tot 3-maal lager in de voorbehandelde groepen dan in de controlegroepen. Het effectieve dosis equivalent buiten de schildklier was aanzienlijk lager bij de met rhTSH voorbehandelde groepen dan bij hun respectievelijke controlegroepen (1,6 maal bij de 0,01 mg rhTSH groep en 2,3 maal bij de 0,03 mg rhTSH groep). Het tijdsbeloop van de eiwit-gebonden ^{131}I activiteit in het serum en de cumulatieve eiwit-gebonden ^{131}I activiteit in het serum verschilden niet significant tussen de met rhTSH voorbehandelde groepen en de controlegroepen.

Uit deze studie kan worden geconcludeerd dat eenmalige toediening van een lage dosis rhTSH gevolgd door behandeling met een gereduceerde dosis ^{131}I conform de rhTSH geïnduceerde toename in 24-uurs RAIU, lagere geabsorbeerde stralingsdoses veroorzaakt in de organen en de weefsels buiten de schildklier, in het bijzonder de blaas en de maag en geen significante stijging van het vrijkomen van ^{131}I-gelabelde schildklierhormonen uit de schildklier in de circulatie bij patiënten met een niet-toxisch, nodulair struma.

7.2

Perspectief

7.2 Perspectief

Op weg naar grotere volumereductie van nodulair struma met ^{131}I: een rol voor voorbehandeling met recombinant humaan TSH?

Een nadeel van behandeling met radioactief jodium voor nodulair struma (waarbij gestreefd wordt naar een na 24 uur geretineerde dosis van ongeveer 100–150 µCi per gram schildklierweefsel) is dat de gemiddelde volumereductie slechts ongeveer 40% na 1 jaar is en dat niet alle patiënten reageren op de behandeling. Eerdere data van Le Moli et al. (1) suggereren dat de volumereductie verbeterd zou kunnen worden door de geabsorbeerde dosis straling in de schildklier te vergroten. Zo'n toename kan worden bereikt door eenvoudig een hogere dosis radioactief jodium toe te dienen, maar dit zal de geabsorbeerde dosis straling in de organen buiten de schildklier ook doen toenemen. Alternatief is om de geabsorbeerde dosis straling in de schildklier te vermeerderen zonder verhoging van de toegediende dosis radioactief jodium, door de opname van het radioactief jodium in de schildklier te stimuleren door middel van voorbehandeling met recombinant humaan TSH (rhTSH).

Een eerste studie over dit onderwerp werd recent gepubliceerd (2). Vierendertig patiënten met een groot, multinodulair struma (80–728 mL), van wie er 22 subklinisch hyperthyreoot en 7 evident hyperthyreoot waren, werden gerandomizeerd in twee groepen. Patiënten uit groep 1 (n = 17) werden behandeld met enkel radioactief jodium, waarbij een eenvoudig doseringsprotocol werd gebruikt (30–50 mCi voor struma <140 g, 58–80 mCi voor struma 150–190 g en 150 mCi voor struma 200-728 g). Patiënten uit groep 2 (n = 17) kregen vergelijkbare doses radioactief jodium 24 uur na voorbehandeling met 0,45 mg rhTSH. Deze rhTSH dosis is hoger dan de dosis die gebruikt werd in onze studies. Schildkliervolumemetingen werden vóór, 6 en 12 maanden na therapie uitgevoerd door middel van CT.

De na 24 uur geretineerde doses radioactief jodium waren 73 ± 12 µCi/g bij de controlepatiënten en 191 ± 75 µCi/g bij de patiënten voorbehandeld met rhTSH. Hogere maximale FT_4-spiegels werden bereikt in groep 2 (59 ± 22 pmol/L, vergeleken met 24 ± 7 pmol/L in groep 1). Het is niet verwonderlijk dat symptomen van thyreoïditis (pijn in het schildkliergebied bij 52% van de patiënten in groep 2, vergeleken met 23% van de patiënten in groep 1) en oesofagitis (17% versus 11%) meer frequent voorkwamen bij de voorbehandelde patiënten. Het is opmerkelijk dat er geen symptomen van hyperthyreoïdie of verergering van hartaandoeningen werden gezien.

Het is interessant dat 1 jaar na therapie de reductie van het schildkliervolume 58 ± 13% bij de patiënten uit groep 2 was in vergelijking met 40 ± 12% bij de patiënten uit groep 1 ($P < 0,05$). De bereikte volumereductie na rhTSH toediening was aanzienlijk groter dan in voorgaande studies zonder rhTSH voorbehandeling waarin doses radioactief jodium werden gebruikt van 100-150 µCi/g.

Hieronder volgt een commentaar op de studie door Silva et al. door onze groep gepubliceerd in het nummer van maart 2004 van Clinical Endocrinology (3):

“ In de laatste twee decennia is aangetoond dat radioactief jodium (^{131}I) een effectieve therapie is ter reductie van het schildkliervolume bij patiënten met een toxisch en niet-toxisch nodulair struma. Bij deze patiënten leidt behandeling met ^{131}I tot een significante afname van de grootte van het struma. Bij de meerderheid van de patiënten verbeteren ook de compressiesymptomen. De afname van de compressiesymptomen gaat gepaard met een significante toename van het lumen van de trachea en een verbetering van de respiratoire functie (4).

Behandeling met ^{131}I is in het bijzonder aantrekkelijk bij oudere patiënten die een hoog operatierisico hebben en/of een operatie weigeren. Bij patiënten met een niet-toxisch, nodulair struma is de opname van radioactief jodium (radioactief jodium uptake; RAIU) echter meestal laag, met name in gebieden met een hoge jodiuminname. Dientengevolge zijn er vaak hoge doses ^{131}I nodig voor de schildklierverkleining, die een relatief hoge stralingsbelasting voor organen buiten de schildklier veroorzaken (5). Het is daarom belangrijk om strategieën te ontwikkelen om de opname van radioactief jodium in de schildklier bij deze patiënten te verhogen.

In de afgelopen tien jaar is rhTSH ter beschikking gekomen voor de diagnostiek bij patiënten met een gedifferentiëerd schildkliercarcinoom. Het is aangetoond dat rhTSH de RAIU in schildklierresten en schildklierkankerweefsel stimuleert (6,7). Recent hebben we gerapporteerd dat rhTSH ook bij patiënten met nodulair struma de RAIU stimuleert; eenmalige toediening een lage dosis van 0,01 mg of 0,03 mg rhTSH verdubbelt de 24-uurs RAIU bij deze patiënten (8). Voorbehandeling met rhTSH zorgt ook voor een meer homogene verdeling van radioactief jodium op het schildklierscintigram van patiënten met een nodulair struma, doordat het de opname van radioactief jodium in de relatief koude gebieden meer stimuleert dan in de relatief warme gebieden, in het bijzonder bij patiënten met een lage serumspiegel van TSH (9). Deze observaties suggereren dat toediening van rhTSH vóór therapie met ^{131}I ter volumereductie van een nodulair struma behandeling met lagere doses ^{131}I mogelijk maakt zonder de geabsorbeerde dosis straling in de schildklier en de effectiviteit van de behandeling te verminderen. Inderdaad zorgde voorbehandeling met één enkele, lage dosis van 0,01 mg of 0,03 mg rhTSH ervoort dat de therapeutische dosis radioactief jodium met 50-60%

verlaagd kon worden zonder dat het resultaat van de volumereductie werd verminderd (10). Aangezien de stralingsbelasting door radioactief jodium van de organen buiten de schildklier direct is gecorreleerd met de toegediende dosis ^{131}I (5), zal zo'n dosisverlaging therapie met radioactief jodium aantrekkelijker maken voor jonge patiënten en zullen meer patiënten poliklinisch kunnen worden behandeld.

Een groot nadeel van therapie met radioactief jodium voor een nodulair struma (waarbij gestreefd wordt naar een na 24 uur geretineerde dosis van ongeveer 100–150 µCi per gram schildklierweefsel) is dat het gemiddelde schildkliervolume met niet meer dan ongeveer 40% afneemt na 1 jaar en met niet meer dan 50-60% na 3-5 jaar (4). Bovendien reageren niet alle patiënten. Eerdere data van Le Moli (1) suggereren dat de volumereductie van het struma kan worden vergroot door de geabsorbeerde dosis radioactiviteit in de schildklier te verhogen. Zo'n toename kan worden bereikt door eenvoudig een hogere dosis radioactief jodium toe te dienen, maar dit zal ook de geabsorbeerde dosis straling in de organen buiten de schildklier doen toenemen. Een alternatief is om de geabsorbeerde dosis straling in de schildklier te vermeerderen zonder verhoging van de toegediende dosis radioactief jodium door de opname van radioactief jodium in de schildklier te stimuleren door middel van voorbehandeling met rhTSH.

Silva et al. (2) beschreven 34 patiënten met grote, nodulaire struma's (22 waren subklinisch hyperthyreoot en 7 evident hyperthyreoot). Deze patiënten werden gerandomiseerd tussen therapie met alleen radioactief jodium of therapie met vergelijkbare doses radioactief jodium in combinatie met voorbehandeling met een relatief hoge dosis rhTSH (0,45 mg) 24 uur vóór de toediening van het radioactief jodium gegeven. Bij de patiënten die werden voorbehandeld met rhTSH was er een significant grotere afname van het schildkliervolume na 1 jaar (58 ± 13%) dan bij de patiënten bij wie radioactief jodium werd gegeven zonder voorbehandeling met rhTSH (40 ± 12%).

Op basis van de beschikbare data uit tabel 1 en 2 in hun artikel hebben we de na 24 uur in de schildklier geretineerde dosis berekend voor de individuele patiënten uit beide groepen. Deze was aanzienlijk hoger bij de rhTSH voorbehandelde patiënten (191 ± 75 µCi per gram schildklierweefsel) dan bij de patiënten die niet waren voorbehandeld met rhTSH (73 ± 22 µCi/g). De grotere afname van het schildkliervolume bij de met rhTSH voorbehandelde groep kan waarschijnlijk worden verklaard door de hogere retentie van radioactief jodium in de

schildklier. Een alternatieve verklaring is dat voorbehandeling met rhTSH de reductie van het schildkliervolume verbetert doordat het een meer homogene verdeling van het radioactief jodium in de schildklier veroorzaakt, met name door het stimuleren van de opname van radioactief jodium in de relatief koude gebieden (9).

Het is te verwachten dat een hogere geretineerde dosis radioactief jodium in de schildklier gepaard zal gaan met ernstigere vroege bijwerkingen door thyreoïditis en oesofagitis. Inderdaad hadden de met rhTSH voorbehandelde patiënten, in vergelijking met de patiënten die niet waren voorbehandeld met rhTSH, een hogere incidentie van pijn in het schildkliergebied (52% versus 23%), klachten door oesofagitis (17% versus 11%) en gewichtsverlies (65% versus 52%).

Een acute vergroting van de schildklier met (toename van) compressie van de trachea is een ander gevolg van thyreoïditis. Uit eerdere studies is gebleken dat één week na therapie met radioactief jodium een toename van het schildkliervolume tot maximaal 25% kan optreden bij doses radioactief jodium waarbij gestreefd wordt naar een na 24 uur geretineerde dosis van ongeveer 100-150 µCi per gram schildklierweefsel (9,11,12). Silva et al. hebben de veranderingen van het schildkliervolume in de eerste periode na de therapie met radioactief jodium niet gemeten. Daarom is het van belang in toekomstige studies te onderzoeken of hogere in de schildklier geretineerde doses ^{131}I, zoals gebruikt door Silva et al., meer toename van het schildkliervolume veroorzaken in de eerste periode na de behandeling met radioactief jodium.

In de eerste weken na behandeling met radioactief jodium van een nodulair struma wordt door straling geïnduceerde thyreoïditis vaak een geringe stijging van de spiegels van schildklierhormonen in het serum gezien, waarbij het maximale niveau ongeveer 2 weken na de therapie wordt bereikt (11). Het is aangetoond dat toediening van lage doses rhTSH (0,01 of 0,03 mg) bij patiënten met een nodulair struma een geringe stijging van schildklierhormoonspiegels in serum veroorzaakt waarbij de maximale waarden 1 tot 4 dagen na toediening van rhTSH worden bereikt (8). Het is te verwachten dat voorbehandeling met een relatief hoge dosis rhTSH gevolgd door een volledige dosis radioactief jodium, leidend tot een hoge dosis in de schildklier geretineerd ^{131}I, meer stijging van de schildklierhormoonspiegels in het serum zal veroorzaken. De maximale FT_4-spiegels bij de met rhTSH voorbehandelde patiënten bestudeerd door Silva et al. waren inderdaad veel hoger dan die bij de patiënten behandeld met alleen

radioactief jodium (59 ± 22 versus 24 ± 7 pmol/L), ondanks een jodium-beperkt diëet voor alle patiënten en voorbehandeling met methimazol bij de 7 evident hyperthyreote patiënten. De hoogste FT_4-spiegel werd al 1 tot 3 dagen na de therapie met radioactief jodium bereikt, hetgeen suggereert dat toediening van rhTSH de belangrijkste oorzaak van de stijging was. Gelukkig werden er geen symptomen van hyperthyreoïdie of verergering van hartaandoeningen gezien. De auteurs geven 3 mogelijke verklaringen: de stijging van de schildklierhormoonspiegels duurde kort, de meeste patiënten gebruikten cardiale medicatie en alle patiënten moesten gedurende 5 tot 9 dagen na de therapie met radioactief jodium bedrust houden.

Een late complicatie van behandeling van nodulair stuma met radioactief jodium is het ontstaan van hypothyreoïdie. Waarschijnlijk houdt dit verband met de hoge dosis radioactief jodium die in de schildklier wordt geretineerd, want Silva et al. vonden dat hypothyreoïdie 1 jaar na therapie met radioactief jodium vaker voorkwam bij de met rhTSH voorbehandelde patiënten dan bij de patiënten die niet waren voorbehandeld met rhTSH (65% versus 21%).

De studie van Silva et al. is de eerste die laat zien dat de effectiviteit van therapie met radioactief jodium bij nodulaire struma's verbeterd kan worden door voorbehandeling met rhTSH. De conclusies zijn echter gebaseerd op een klein aantal patiënten waarbij zowel patiënten met een toxisch (4 van hen hadden amiodarone gebruikt) als patiënten met een niet-toxisch struma werden geïncludeerd. Bovendien is er geen poging gedaan om de doses radioactief jodium te berekenen (de doses radioactief jodium werden gebaseerd op een nogal simpel algoritme met als enige parameter het palpatoir geschatte schildkliervolume).

Voordat rhTSH kan worden geadviseerd als adjuvans om de effectiviteit van therapie met radioactief jodium bij nodulair struma te verbeteren zijn meer studies nodig. Allereerst moet in een formele dosis-respons studie worden vastgesteld welke dosis rhTSH optimaal is voor dit doel. Zo'n dosis moet de RAIU aanzienlijk stimuleren maar mag geen onacceptabele verhoging van de schildklierhormoonspiegels in het serum veroorzaken. Daarna moet therapie met radioactief jodium met en zonder die dosis rhTSH worden onderzocht in gerandomiseerde studies, waarin zorgvuldig de dosis-respons relaties met betrekking tot effectiviteit en bijwerkingen bestudeerd moeten worden. Gezien de heterogeniteit van nodulaire struma's zullen grote groepen patiënten nodig zijn. ”

Recent werden twee studies gepubliceerd waarin de resultaten werden beschreven van poliklinische behandeling van patiënten met een niet-toxisch, nodulair struma met een dosis van 30 mCi ^{131}I na stimulatie met rhTSH. Duick and Baskin (13) gaven aan 6 patiënten 0,3 mg rhTSH 72 uur vóór de therapie met radioactief jodium en aan 10 patiënten 0,9 mg rhTSH 24 uur vóór de therapie met radioactief jodium. Het schildkliervolume vóór de behandeling bedroeg 81 ± 25 mL. Bij de 6 patiënten die 0,3 mg rhTSH kregen verviervoudigde de 4-uurs radioactief jodium opname 72 uur na rhTSH (van 4 ± 1% naar 17 ± 8%). De geschatte verkleining van het schildkliervolume was 30–40% na 3–7 maanden bij 15 van de 16 patiënten.

Graf en medewerkers (14) gaven aan 26 patiënten 2 injecties met 0,1 mg rhTSH 48 en 24 uur vóór therapie met radioactief jodium. Het basale schildkliervolume was 116 ± 37 ml. De 24-uurs opname van de dosis radioactief jodium, 24 uur na de laatste dosis rhTSH toegediend, verviervoudigde (van 12 naar 54%). De FT_4-spiegels stegen 24 uur na de laatste dosis rhTSH tot maximaal 3,2 ± 1,1 ng/dL. De gemiddelde afname van het met CT gemeten schildkliervolume bedroeg 39% na 6 maanden.

Voordat rhTSH kan worden geadviseerd als adjuvans om de effectiviteit van therapie met radioactief jodium bij nodulair struma te verbeteren, moeten twee belangrijke vragen worden beantwoord. Om te beginnen weten we de optimale dosis rhTSH voor deze indicatie op dit moment nog niet. Deze dosis moet geen onacceptabele stijging van de schildklierhormoonspiegels in het serum en toename van het schildkliervolume veroorzaken maar anderzijds wel de opname van radioactief jodium substantiëel stimuleren en zorgen voor een meer homogene verdeling van het radioactief jodium in de schildklier.

Het zorgvuldig vaststellen van de veiligheid van de toediening van rhTSH aan patiënten met een nodulair struma is een zeer belangrijk punt, aangezien injectie van rhTSH bij mensen met functionerend schildklierweefsel een stijging van de schildklierhormoonspiegels en een toename van het schildkliervolume veroorzaakt. In een recente studie (15) leidde toediening van 0,9 mg rhTSH aan gezonde vrijwilligers tot een verdubbeling van de serumspiegels van FT_4 en een toename van het schildkliervolume met 35%. Het maximale effect werd 48 uur na de toediening van rhTSH gezien.

De tweede vraag die beantwoord moet worden is welke dosis straling voor de schildklier (in geretineerd aantal μCi per gram schildklierweefsel) optimaal is, zowel wat betreft veiligheid (minimale stijging van de schildklierhormoonspiegels en toename van het schildkliervolume door het radioactief jodium op korte termijn) als wat betreft de effectiviteit (verkleining van het schildkliervolume op lange termijn).

Zoals boven besproken zijn er vrijwel geen data beschikbaar met betrekking tot de hypothese dat verhoging van de geretineerde activiteit in de schildklier naar een niveau boven de 100-150 µCi/g schildklierweefsel na 24 uur, met of zonder stimulatie door rhTSH, de effectiviteit van therapie met radioactief jodium bij nodulair struma verbetert.

We concluderen daarom dat er meer onderzoek nodig is voordat rhTSH kan worden geadviseerd als adjuvans om de effectiviteit van behandeling met radioactief jodium ter verkleining van nodulaire struma's te verbeteren. Het doel van zulke fase II en III studies zou moeten zijn het vinden van aanwijzingen respectievelijk definitief bewijs, dat verhoging van de geretineerde activiteit in de schildklier door voorbehandeling met rhTSH veilig is en resulteert in een grotere volumeafname van de schildklier. In deze studies zou een vaste hoeveelheid (bijvoorbeeld 15 of 30 mCi) of een berekende hoeveelheid radioactief jodium kunnen worden gebruikt.

Referenties

1 **Le Moli R, Wesche MFT, Tiel-van Buul MMC, Wiersinga WM** 1999 Determinants of longterm outcome of radioiodine therapy of sporadic non-toxic goitre. Clin Endocrinol (Oxf) 50:783-789

2 **Silva MN, Rubio IG, Romao R, Gebrin EM, Buchpiguel C, Tomimori E, Camargo R, Cardia MS, Medeiros-Neto G** 2004 Administration of a single dose of recombinant human thyrotrophin enhances the efficacy of radioiodine treatment of large compressive multinodular goitres. Clin Endocrinol (Oxf) 60:300-308

3 **Huysmans DA, Nieuwlaat W-A, Hermus AR** 2004 Towards larger volume reduction of nodular goitres by radioiodine therapy: a role for pretreatment with recombinant human thyrotropin? Clin Endocrinol (Oxf) 60:297-299

4 **Hegedüs L, Bonnema SJ, Bennedbæk FN** 2003 Management of simple nodular goiter: current status and future perspectives. Endocr Rev 24:102-132

5 **Huysmans DAKC, Buijs WCAM, van de Ven MTP, van den Broek WJM, Kloppenborg PWC, Hermus ARMM, Corstens FHM** 1996 Dosimetry and risk estimates of radioiodine therapy for large, multinodular goiters. J Nucl Med 37:2072-2079

6 **Ladenson PW, Braverman LE, Mazzaferri EL, Brucker-Davis F, Cooper DS, Garber JR, Wondisford FE, Davies TF, DeGroot LJ, Daniels GH, Ross DS, Weintraub BD** 1997 Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N Engl J Med 337:888-896

7 **Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, Cooper DS, Graham KE, Braverman LE, Skarulis MC, Davies TF, DeGroot LJ, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Becker DV, Maxon HR, III, Cavalieri RR, Spencer CA, McEllin K, Weintraub BD, Ridgway EC** 1999 A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J Clin Endocrinol Metab 84:3877-3885

8 **Huysmans DA, Nieuwlaat W-A, Erdtsieck RJ, Schellekens AP, Bus JW, Bravenboer B, Hermus AR** 2000 Administration of a single low dose of recombinant human thyrotropin significantly enhances thyroid radioiodide uptake in nontoxic nodular goiter. J Clin Endocrinol Metab 85:3592-3596

9 **Nieuwlaat W-A, Hermus AR, Sivro-Prndelj F, Corstens FH, Huysmans DA** 2001 Pretreatment with recombinant human TSH changes the regional distribution of radioiodine on thyroid scintigrams of nodular goiters. J Clin Endocrinol Metab 86:5330-5336

10 **Nieuwlaat W-A, Huysmans DA, van den Bosch HC, Sweep CG, Ross HA, Corstens FH, Hermus AR** 2003 Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. J Clin Endocrinol Metab 88:3121-3129

11 **Nygaard B, Faber J, Hegedüs L** 1994 Acute changes in thyroid volume and function following 131I therapy of multinodular goitre. Clin Endocrinol (Oxf) 41:715-718

12 **Bonnema SJ, Bertelsen H, Mortensen J, Andersen PB, Knudsen DU, Bastholt L, Hegedüs L** 1999 The feasibility of high dose iodine 131 treatment as an alternative to surgery in patients with a very large goiter: effect on thyroid function and size and pulmonary function. J Clin Endocrinol Metab 84:3636-3641

13 **Duick DS, Baskin HJ** 2003 Utility of recombinant human thyrotropin for augmentation of radioiodine uptake and treatment of nontoxic and toxic multinodular goiters. Endocr Pract 9:204-209

14 **Graf H, Mesa CO, Albino CC** 2003 Radioactive Iodine (^{131}I) in Multinodular Goiter (MNG) Treatment with the Aid of Recombinant Human TSH (rhTSH, Thyrogen®). Program Number 174, Annual 75th Meeting of the American Thyroid Association 2003, Palm Beach, FL, September 16-21:726

15 **Nielsen VE, Bonnema SJ, Hegedüs L** 2004 Effects of 0.9 mg recombinant human thyrotropin on thyroid size and function in normal subjects: a randomized, double-blind, cross-over trial. J Clin Endocrinol Metab 89:2242-2247

chapter

8

8.1

Dankwoord

8.1

Dankwoord

Het verrichten van wetenschappelijk onderzoek is vooral teamwork. Aan dit onderzoek hebben mensen uit verschillende disciplines en op diverse locaties hun bijdragen geleverd. Een groot aantal wil ik dan ook bedanken voor hun medewerking aan dit project: allereerst de promotores Ad Hermus, de grondlegger van de gehele onderneming, die vertrouwen gaf en geduld; Frans Corstens, voor het verlenen van zijn samenwerking en de co-promotor Dyde Huysmans, die zich altijd zeer genereus en oordeelkundig heeft getoond. Dat ik van hun wijsheid heb mogen profiteren is van onschatbare waarde geweest.

Bij de uitvoering van het onderzoek zijn de patiënten, die hebben meegewerkt op de Afdeling Nucleaire Geneeskunde van het Catharina Ziekenhuis, de hoeksteen geweest. Ik heb het geweldige geluk gehad gebruik te mogen maken van de overweldigende hulp en het enthousiasme van Jo Bus, zonder wie dit onderzoek nooit had kunnen plaatsvinden. Veel werk werd onder haar leiding verricht door Karin van Assen. De nucleair geneeskundigen Ferida Sivro-Prndelj en Michela Edelbroek, alle nucleair laboranten, Bernie Gitmans en Chris Jansen en bovenal "onze" Ans gaven in Eindhoven altijd weer een duwtje in de rug. Voor het uitvoeren van de laboratoriumbepalingen sta ik bij Andries Schellekens en voor de MRI's bij Harrie van den Bosch in het krijt. Telkens weer maakten zij tijd en plaats voor ons.

Bijzondere dank is verschuldigd aan de medewerkers van de afdeling Chemische Endocrinologie in het Universitair Medisch Centrum St. Radboud. Zowel voor vakkundige laboratoriumbepalingen, als allerlei "hand en span" diensten stonden zij garant. Met name Fred Sweep, Alec Ross en Tijn Segers hebben mij uit de nood geholpen wanneer het er echt op aankwam.

Op de afdeling Nucleaire Geneeskunde in het Universitair Medisch Centrum St. Radboud, kon ik altijd weer terecht voor een deskundig advies. Als "buitenstaander" heb ik dankzij Wim van den Broek, Otto Boerman en Wil Buijs de ingangen van de Nucleaire Geneeskunde leren kennen. Ook tegen Ernst Postema zeg ik "grazie": het tegelijkertijd bezig zijn met promotie-onderzoek gaf altijd stof voor een goed gesprek.

Bij de uitvoering van de muizenexperimenten heb ik gebruik mogen maken van de fenomenale handvaardigheden van Gerry Grutters op het Centraal Dieren Laboratorium en de bepalingen door Jan Smit op de afdeling Endocrinologie van het Leids Universitair Medisch Centrum (waarvan de uitslagen telkens weer als "attentie" of "cadeau" werden gemailed).

Voorts heb ik het bijzonder plezierig gevonden tijdens de uitvoering van dit wetenschappelijk onderzoek op de afdeling Endocriene Ziekten in het Universitair Medisch Centrum St. Radboud te mogen samenwerken met Gerlach Pieters, Martin den Heijer, Marie-José Pouwels, Sarah Bovenberg, Anita Peeters en Romana Netea-Maier. Voor hun contacten en collegialiteit ben ik hen zeer erkentelijk. Mijn kamergenoten op de Afdeling Endocriene Ziekten zorgden voor een aangename sfeer, hiervoor bedank ik Stan van Uum, Lieke Hoogendoorn en Egidia van Ginneken. Het was fijn met hen allen samen te werken op een hoog professioneel niveau. Dit kon dan ook alleen gebeuren dankzij de fantastische secretariële ondersteuning van Wil Straten, Lennie Scholte en Mieke van Haaren.

Op dit moment ben ik mijn maten: Fred Apperloo, Marina Grubben, Cees van der Heul, Job Juttmann, Marjo van Kasteren, Marc van Milligen de Wit, Wiek Rensma, Anne-Marie van Riel, Wouter Stuifbergen en Saskia van Veen, mijn secretaresse Drea van Spaendonk, de diabetes-verpleegkundigen José Jacobs, Kim de Jong en Judith Schaffels en de arts-assistenten Interne Geneeskunde in het Sint Elisabeth Ziekenhuis, duizend maal dank (“mille grazie”) verschuldigd voor hun support tijdens de laatste loodjes ter afronding van “het boekje” en hun bijna wekelijks terugkerende vraag wanneer “het feest” zou plaatsvinden.

Dankzij de paranimfen Dave van Kraaij en Marika van Leeuwen-Artz kunnen de festiviteiten dan nu eindelijk beginnen. Wat is het fijn om goede vrienden te hebben! Maar bovenal ben ik mijn familie dankbaar. Hoe kan ik de steun van mijn ouders omschrijven? Voor alle hulp dank ik hen en de rest van mijn familie.

Tot slot bedank ik in stilte de mensen, die mij in discretie hebben bijgestaan, en zonder wie geen enkel verhaal wordt geschreven.

8.2

Curriculum Vitae

8.2

Curriculum Vitae Nederlands

Willy-Anne Nieuwlaat werd op 25 oktober 1969 geboren te Roosendaal. Van 1982 tot 1988 bezocht zij aldaar het Gertrudislyceum en behaalde het diploma Gymnasium β.

In 1988 begon zij met de studie geneeskunde aan de Radboud Universiteit Nijmegen. In 1989 werd de Propedeuse en in 1992 het Doctoraalexamen *cum laude* afgelegd. Op 28 april 1995 volgde het Artsexamen.

Van mei 1995 tot en met augustus 1999 was zij werkzaam als arts-assistent Interne Geneeskunde in het Canisius-Wilhelmina Ziekenhuis te Nijmegen, aanvankelijke als Assistent Geneeskundige Niet In Opleiding. Op 1 augustus 1996 werd in het CWZ begonnen met de opleiding Interne Geneeskunde (Opleider: Dr. R.W. de Koning). Deze opleiding werd voortgezet in het Universitair Medisch Centrum St. Radboud te Nijmegen (Opleider: Prof.dr. J.W.M. van der Meer) en op 1 augustus 2002 vond registratie als Internist plaats.

In het aandachtsgebied Endocrinologie werd zij vanaf maart 2002 tot september 2003 op de afdelingen Endocriene Ziekten en Algemeen Interne Geneeskunde (Opleiders: Prof.dr. A.R.M.M. Hermus en Prof.dr. J.A. Lutterman) van het Universitair Medisch Centrum St. Radboud opgeleid.

Sinds oktober 2003 is zij als internist-endocrinoloog werkzaam in het Sint Elisabeth Ziekenhuis te Tilburg.

Curriculum Vitae English

Willy-Anne Nieuwlaat was born on October 25, 1969 in Roosendaal, The Netherlands. From 1982 until 1988 she visited the Gertrudislyceum there and graduated from Gymnasium β.

In 1988 she began her study of medicine at the Medical Faculty of the Radboud University Nijmegen. In 1989 the "Propedeuse" and in 1992 the "Doctoraalexamen" in medicine were passed *with honor*. Her medical license (Artsexamen) was obtained on April 28, 1995.

From May 1995 until August 1999 she worked as a hospital-based physician at the Department of Internal Medicine of the Canisius-Wilhelmina Hospital in Nijmegen. On August 1, 1996 she began her residency training in Internal Medicine. The first portion of the training was undertaken at this same hospital under the supervision of Dr. R.W. de Koning. The training program continued at the Radboud University Nijmegen Medical Center under the supervision of Prof.dr. J.W.M. van der Meer. On August 1, 2002 she was registered as Specialist in Internal Medicine.

A fellowship in Endocrinology was completed between March 2002 and September 2003 at the Departments of Endocrinology and General Internal Medicine of the Radboud University Nijmegen Medical Center under the direction of Prof.dr. A.R.M.M. Hermus and Prof.dr. J.A. Lutterman.

Since October 2003, she has been working as an internist-endocrinologist at Saint Elisabeth Hospital in Tilburg.

8.3

List of Publications

8.3

List of Publications

1 Huysmans DA, **Nieuwlaat W-A**, Hermus AR.
Recombinant human thyrotropin (Thyrogen®):
a potential adjunct to radioiodine therapy for nontoxic goiter.
In: Brochocele (Goiter) - Genesis upon the Advent of the New Millenium - from molecular biology to clinical assessment; Thyroid Congress under the auspices of the European Thyroid Association.
Proceedings of congress; May 11-13, 2000; Athens, Greece.

2 Huysmans DA, **Nieuwlaat W-A**, Erdtsieck RJ, Schellekens AP, Bus JW, Bravenboer B, Hermus AR.
Administration of a single, low dose of recombinant human thyrotropin significantly enhances thyroid radioiodide uptake in nontoxic, nodular goiter.
The Journal of Clinical Endocrinology and Metabolism 2000 Oct; 85(10):3592-3596.

3 **Nieuwlaat W-A**, Hermus AR, Sivro-Prndelj F, Corstens FH, Huysmans DA.
Pretreatment with recombinant human TSH changes the regional distribution of radioiodine on thyroid scintigrams of nodular goiters.
The Journal of Clinical Endocrinology and Metabolism 2001 Nov; 86(11):5330-5336.

4 Span PN, Sleegers MJM, van den Broek WJ, Ross HA, **Nieuwlaat W-A**, Hermus ARMM, Sweep CGJ.
Quantitative detection of peripheral thyroglobulin mRNA has limited clinical value in the follow-up of thyroid cancer patients.
Annals of Clinical Biochemistry 2003 Jan; 40(1):94-99.

5 **Nieuwlaat W-A**, Hermus AR, Huysmans DA.
Nontoxic, nodular goiter: new management paradigms.
The Endocrinologist 2003 Jan-Feb; 13(1):31-37.

6 **Nieuwlaat W-A**, Huysmans DA, van den Bosch HC, Sweep CG, Ross HA, Corstens FH, Hermus AR.
Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter.
The Journal of Clinical Endocrinology and Metabolism 2003 Jul; 88(7):3121-3129.

"Marie Curie Award" nomination at the European Association of Nuclear Medicine Congress 2002; August 31-September 4; Vienna, Austria.
"Prize-winner Research Internist-Days 2003" at the NIV (Netherlands Association of Internal Medicine), 15th Internist-Days 2003; May 14-16; Maastricht, The Netherlands.
"Prize-winner The Best Article Clinical Endocrinology 2003" at the NVE (Netherlands Association for Endocrinology) and NVDO (Netherlands Association for Diabetes Research), 14th Meeting Clinical Endocrinology 2004; February 6-7; Doorwerth, The Netherlands.

7 **Nieuwlaat W-A**, Huysmans DA, Hermus AR.
Authors' response: Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter.
The Journal of Clinical Endocrinology and Metabolism 2003 Dec; 88(12):6114-6115.

8 Huysmans DA, **Nieuwlaat W-A**, Hermus AR.
Commentary. Towards larger volume reduction of nodular goitres by radioiodine therapy: a role for pretreatment with recombinant human thyrotropin?
Clinical Endocrinology 2004 Mar; 60(3):297-299.

9 **Nieuwlaat W-A**, Hermus AR, Ross HA, Buijs WC, Edelbroek MA, Bus JW, Corstens FH, Huysmans DA.
Dosimetry of radioiodine therapy in patients with nodular goiter after pretreatment with a single, low dose of recombinant human thyroid-stimulating hormone.
The Journal of Nuclear Medicine 2004 Apr; 45(4):626-633.

10 **Nieuwlaat W-A**, Pieters G.
A medical mystery – Which twin is the patient?
(Images in Clinical Medicine).
The New England Journal of Medicine 2004 Jul; 351(1):68.

11 **Nieuwlaat W-A**, Pieters G.
Medical mystery – The Answer (Correspondence).
The New England Journal of Medicine 2004 Aug; 351(8):835-836.