CLINICAL STUDY

Low-dose recombinant human thyrotropin-aided radioiodine treatment of large, multinodular goiters in elderly patients

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Abstract

Objective: We aimed to assess low-dose recombinant human thyroid-stimulating hormone (rhTSH)-aided, fixed-activity radioiodine therapy of large, multinodular goiters (MNGs) in elderly patients with comorbidities.

Design: This was a short-term, observational study.

Methods: We measured 24-h thyroid radioiodine uptake (RAIU) of 2 μ Ci 131-iodine at baseline and 24 h after intramuscular injection of 0.03 mg rhTSH in 17 patients (aged 60–86 years, 12 women), who subsequently received 30 mCi 131-iodine 24 h after an identical rhTSH injection. TSH and free thyroxine (FT₄) were measured at baseline and days 10, 30 and 90 after therapy. Thyroid volume was assessed by computed tomography at baseline and day 180.

Results: rhTSH, 0.03 mg, significantly increased mean 24-h thyroid RAIU from 25.8% $\pm$ 10.3% to 43.3% $\pm$ 8.4% (68% relative increase; $t(16) = -8.43$, $P < 0.001$). The proportion of patients overtly or subclinically hyperthyroid (TSH < 0.5 mU/l) decreased from 71% (12/17) at baseline to 19% (3/16) at 3 months. Mean serum FT₄ peaked at slightly above normal range, 25.9 $\pm$ 7.7 pmol/l (46% over baseline) and was 21% under baseline levels at 3 months. Mean estimated thyroid volume fell 34% from baseline to 6 months (170.0 $\pm$ 112.8 to 113.1 $\pm$ 97.5 ml; $P < 0.01$). Symptomatic relief, improved well-being, and/or reduction or elimination of antihyperthyroid medication were seen in 76% of patients. Three (18%) patients had transient neck pain or tenderness, or palpitations; one had transient asymptomatic thyroid enlargement; and three (18%) became hypothyroid by 3 months.

Conclusions: Intramuscular rhTSH, 0.03 mg, followed 24 h later by 30 mCi 131-iodine, is a safe, effective and convenient treatment for MNG in elderly patients with comorbidities.

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Introduction

The prevalence of multinodular goiter (MNG) rises in the elderly (1, 2), a population in whom comorbidities prevail. The natural history of MNG sometimes entails a size increase with age, retrosternal extension of the goiter causing compressive and obstructive symptoms, principally airway compromise and swallowing difficulty. Of even greater concern, in iodine-replete areas, subclinical or overt hyperfunctioning of the thyroid gland often develops. Thyroid hyperfunctioning is associated with accelerated bone loss, atrial arrhythmia, and cardiac hypertrophy, markedly increasing the mortality rate in elderly goiter patients with suppressed serum thyroid-stimulating hormone (TSH) (3, 4).

Thus treatment of MNG in the elderly typically must be aimed not just at the compressive symptoms, but also the thyroid hyperfunction, whether clinical or subclinical. Suppressing thyroid hormone therapy is controversial because it leads at best to modest and temporary goiter size reduction and of course brings about hyperthyroidism (1). Surgery is the treatment of choice for its favorable results in reducing goiter size, rapidly relieving hyperthyroidism and removing incidentally discovered malignancy (1, 5, 6). However, elderly patients and their physicians are sometimes reluctant to employ surgery for fear of complications due to the large goiter and age-related comorbidities.

Radioiodine therapy is a nonsurgical treatment of MNG (1, 6–9), lately shown to be effective in very large, symptomatic goiters (10). The convenience

of this single, noninvasive, low-cost procedure is fraught with several caveats. For one, the efficiency of treatment is attenuated with increasing goiter size (10). Moreover, radioiodine-induced hyperthyroidism immediately after treatment can occur in up to 15% of cases due to direct injury of thyroid follicles or secondary to radiation-induced thyroiditis (1). Iatrogenic hyperthyroidism counters the goal of preventing cardiac arrhythmia in the elderly. Other potential untoward effects of radioiodine treatment include transient thyroid edema with increased compressive symptoms, and tumorigenicity. Both these complications are dose-dependent (11), and this is especially relevant considering the high ^{131}I activities frequently used to treat MNG. For example, in large goiters, the median ^{131}I activity applied in a recent study was 61.6 mCi (10).

Preadministration of recombinant human (rh) TSH to increase the amount and homogeneity of radioiodine uptake (RAIU) in the nodular goiter might augment the efficiency of ^{131}I therapy (12, 13). At the same time, rhTSH stimulation can improve the safety of radioiodine treatment by allowing decreased ^{131}I activity. Indeed, a recent study showed that by permitting a marked ^{131}I activity reduction, rhTSH stimulation significantly lowered extrathyroidal radiation-absorbed doses, especially in the bladder and stomach (14).

At the time of the present study, published trials of rhTSH in MNG had shown promising results. However, these studies utilized ^{131}I activity calculation (14, 15), a method that may be impractical in many settings, or high doses of rhTSH (16, 17), which may transiently exacerbate post-therapeutic hyperthyroidism. We therefore conducted the present short-term, observational study to assess the safety and efficacy of low-dose rhTSH stimulation of a fixed low radioiodine activity in the treatment of large MNGs in elderly patients with comorbidities.

Patients and methods

Patients

Study inclusion criteria were MNG causing compressive symptoms, age of at least 60 years, and inability or unwillingness to undergo thyroidectomy. Seventeen patients (14 women; median age, 71 years, range 60–85 years) with large, long-standing MNG (median volume, 170.1 ml, range, 60.4–485.9 ml) were referred for treatment. Twelve had overt or subclinical hyperthyroidism, defined as $\text{TSH} < 0.5 \text{ mU/l}$, in five cases requiring thionamides (propylthiouracil or mercaptizol). All patients were radioiodine- and thyroid hormone suppression therapy-naïve, and 14 (82%) had never undergone thyroid surgery. Table 1 describes baseline patient characteristics and comorbidities.

Thirteen patients were high-risk candidates for thyroidectomy due to comorbidity (Table 1), while two

patients each refused surgery or had a prior neck operation leading the surgeon to prefer a noninvasive procedure. All but one patient had undergone ultrasound-guided fine-needle aspiration cytology of dominant nodules to rule out malignancy.

Ethical considerations

The study protocol was approved for 'off-label' use of recombinant TSH by the hospital's pharmacology review board. All patients provided written, informed consent.

Study design

Figure 1 depicts the study design. Unstimulated 24-h thyroid RAIU was measured at baseline, defined as 3 months to 2 weeks before rhTSH-aided RAIU measurement. rhTSH-aided RAIU was measured on day 8 before the study. Patients were to be removed from study if rhTSH failed to increase RAIU beyond 10%. rhTSH-aided radioiodine treatment was given 8 days after administration of the rhTSH-aided test activity.

At baseline, patients also underwent thyroid function testing (TFT), that is, measurement of serum levels of TSH, free L-thyroxine (FT_4) and total triiodothyronine (TT_3), and assessment of thyroid volume and tracheal diameter. TFT was repeated on days 10, 30 and 90 after therapy, and thyroid volume and tracheal diameter measurement on day 180. The change in laboratory and clinical thyroid function from baseline to day 90 was the primary efficacy endpoint, and the change in thyroid volume and tracheal diameter from baseline to day 180 were the secondary efficacy endpoints of the study.

Safety was monitored via routine laboratory tests, physical examination and clinical observation. We also queried patients about their recent health at each clinic visit, and instructed them to report any adverse events at any time during the study.

Patients were taken off thionamides for the 10 days before all radioiodine administrations.

Twenty-four-hour thyroid RAIU

For measurement of unstimulated (baseline) 24-h thyroid RAIU, patients were given a test activity of $2 \mu\text{Ci } ^{131}\text{I}$ as an oral capsule. The uptake measurements were performed with a standard probe using a 364 keV ^{131}I window. Twenty-four hours after ^{131}I administration, a 10 mCi activity of technetium-99m-pertechnetate (Tc-99m) was administered intravenously, and an anterior-view thyroid scan was performed, accumulating 400 000 counts in the $140 \pm 10 \text{ keV Tc-99m}$ window, using a SP4 APEX gamma camera (Elsint/GE Co, Haifa, Israel) equipped with a pinhole collimator.

Table 1 Baseline clinical characteristics.

Patient no.	Sex	Age	Signs, symptoms and thyroid-related medication	Comorbidities and medical history
1	F	66	Hyperthyroidism; thyrotoxicosis requiring thionamide therapy	Diabetes mellitus
2	F	71	None	None
3	F	79	None	None
4	M	74	Hyperthyroidism	Extrapyramidal neurologic disorder
5	F	66	Hyperthyroidism	Diabetes mellitus, hypertension
6	F	60	Hyperthyroidism	Diabetes mellitus, hyperthyroidism evolving from Hashimoto's thyroiditis
7	F	85	Hyperthyroidism	Coronary artery disease, s/p pulmonary emboli, chronic obstructive pulmonary disease
8	M	81	Hyperthyroidism, thionamide therapy, paroxysmal atrial fibrillation	Coronary artery disease, chronic obstructive pulmonary disease, chronic renal failure
9	F	74	Hyperthyroidism	Hypertension, coronary artery disease, peripheral vascular disease, history of coronary artery bypass grafting
10	F	60	None	Diabetes mellitus with severe complications
11	F	66	None	Diabetes mellitus with complications, s/p left hemithyroidectomy
12	F	69	Hyperthyroidism, thionamide therapy, paroxysmal atrial fibrillation	History of breast cancer
13	F	73	Hyperthyroidism, thionamide therapy	Hyperlipidemia
14	M	69	Hyperthyroidism, thionamide therapy	Diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease, obesity, smoker
15	F	80	Hyperthyroidism	Hypertension, chronic obstructive pulmonary disease
16	F	83	Hyperthyroidism	Hypertension, hyperlipidemia, s/p right hemithyroidectomy
17	F	63	None	s/p hemithyroidectomy

s/p = status post.

Measurement of rhTSH-aided 24-h RAIU was performed in the same manner by the same observers, except that each patient received an intramuscular injection of 0.03 mg rhTSH (Thyrogen; Genzyme, Cambridge, MA, USA) 24 h before ^{131}I administration. This rhTSH dose was chosen as the apparently more active of the two lowest rhTSH doses reported in the goiter setting (13). All injections were prepared freshly by dilution in saline of the original 1.1 mg ampoule.

TFT

Serum TSH, FT_4 and TT_3 levels were determined by a chemiluminescent immunometric assay (Immulate;

DPC, Los Angeles, CA, USA). The normal ranges were 0.4–4.0 mU/l for TSH, 10.0–25.0 pmol/l for FT_4 and 1.1–2.6 nmol/l for TT_3 . The interassay coefficients of variation were 3–12% for TSH, 4–10% for FT_4 and 6–10% for TT_3 .

Thyroid volume and tracheal diameter

Thyroid volume was estimated, and tracheal diameter measured, by the same observer (C H) using non-contrast-enhanced computed tomography (CT) images of the neck and mediastinum. Images were obtained

Figure 1 Study design. CT, computed tomography; PE, physical examination; RAIU, radioiodine uptake; rhTSH, recombinant human thyroid-stimulating hormone; TFT, thyroid function test.

at various local centers, but, for each patient, were taken on the same plane of maximal size by the same operator using the same equipment. Planar and axial images were reconstructed with a standard algorithm, and post-processing was performed on a commercially available workstation.

Thyroid volume calculations were based on the model of a rotation ellipsoid modified as the sum of the two lobes' width $\times$ thickness $\times$ length $\times \pi/6$. The normal range for thyroid volume estimated by this method is 5–30 ml in adults (18). Tracheal diameter was calculated at the narrowest cross section. All thyroid volume estimations and tracheal diameter calculations were performed with the observer blinded as to whether the CT image was taken before or after rhTSH-aided radioiodine treatment.

Treatment protocol

Twenty-hour hours after intramuscular injection of 0.03 mg rhTSH, administered as described above, patients received a fixed therapeutic activity of ~ 30 mCi ^{131}I given as a single oral dose to an outpatient. A fixed activity was chosen for simplicity and 30 mCi because it is the maximum outpatient activity allowed in Israel.

Statistical analyses

The mean $\pm$ s.d. values are given for mean TFT, thyroid volume and tracheal diameter results. Statistical analyses used the *t*-test for dependent samples by groups or by absolute changes. The level of significance was 0.05.

Results

Twenty-four-hour RAIU and uptake distribution

Table 2 shows individual unstimulated (baseline) and rhTSH-stimulated RAIU for the study population. A single injection of 0.03 mg rhTSH significantly increased mean 24-h thyroid RAIU from $25.8\% \pm 10.3\%$ to $43.3\% \pm 8.4\%$ (relative increase of 68%; $P < 0.001$). Individual relative percentage increases in uptake ranged from 22.1% to 847.9% and averaged $116.0 \pm 68.2\%$. All patients exhibited an increase in uptake greater than 10% after rhTSH stimulation, and therefore were considered suitable for rhTSH-aided radioiodine therapy.

As determined by qualitative, within-patient comparison, thyroid scans in most patients showed a more homogeneous distribution of the material after rhTSH administration (representative images shown in Fig. 2). As previously described (13), the more homogeneous uptake distribution after rhTSH was attributable to increased uptake in nonautonomous areas that at baseline did not concentrate iodine.

Thyroid function – laboratory results

Table 3 presents individual baseline, peak and final (3-month) TFT results, while Fig. 3 represents individual FT_4 measurements during the study. TSH levels were below normal range (subclinical or overt hyperthyroidism) in 12 of the 17 patients (71%) at baseline and in 16 of the 17 patients by day 10 after therapy (data not shown). However, at the final TSH measurement, only 3/16 (19%) patients with available

Table 2 Effect of 0.03 mg rhTSH on 24-h RAIU.

Patient no.	% uptake without rhTSH	% uptake 48 h after rhTSH injection	Relative percentage change
1	18.6	32.0	72.0
2	22.0	30.1	36.8
3	38.5	47.0	22.1
4	21.0	38.2	81.9
5	22.0	32.1	45.9
6	24.8	38.9	56.9
7	16.0	38.0	137.5
8	4.8	45.5	847.9
9	44.0	56.0	27.3
10	14.0	46.8	234.3
11	39.0	57.0	46.2
12	22.0	36.1	64.3
13	36.9	52.7	42.8
14	31.6	47.0	48.7
15	34.0	46.0	35.3
16	28.0	52.4	87.1
17	21.0	40.8	94.3
Mean $\pm$ s.d.	25.8 ± 10.3	43.4 ± 8.4	68.2%

RAIU, radioiodine uptake; rhTSH, recombinant human thyroid-stimulating hormone.

Figure 2 Representative scan (of patient no. 13) using a gamma camera, obtained 10 min after i.v. injection of Tc-99m pertechnetate isotope, showing Tc-99m distribution without TSH stimulation (left image) and 48 h after injection of 0.03 mg rhTSH (right image). rhTSH administration markedly increased Tc-99m uptake throughout the right lobe and, even more prominently, the left lobe.

values had subnormal TSH levels (subclinical hyperthyroidism).

From baseline to day 10 after therapy, mean serum FT_4 increased 33% (from 17.8 ± 5.7 to 23.6 ± 7.1 pmol/l) ($P < 0.01$). During this time, 16 patients experienced FT_4 increases, which ranged from 2% to 120%. At baseline, only one patient had FT_4 above normal range, but at day 10, that patient and four others did. However, only the patient thyrotoxic at baseline and one other patient had day-10 levels above the 30 pmol/l concentration that is considered overtly hyperthyroid.

Mean serum FT_4 peaked at slightly above normal range, at 25.9 ± 7.7 pmol/l, a level 46% higher than at baseline. Peak FT_4 exceeded baseline concentrations in all 17 patients; increases ranged from 12% to 176%. The maximal peak values in the study population were 41.4 and 41.1 pmol/l. However, final (3-month) mean FT_4 levels were decreased 21% from baseline (17.8 ± 5.5 pmol/l, $n = 17$ at baseline, vs 14.0 ± 5.6 pmol/l, $n = 14$ at 3 months; $P < 0.1$). The mean individual change in FT_4 from baseline to 3 months was $-22\% \pm 30\%$ ($n = 14$). Thirteen of 14 evaluable patients experienced decreases from baseline to 3 months, ranging from 4% to 48%, and one had a 71% increase (but remained within the normal range).

Mean serum TT_3 peaked within the normal range at 2.8 ± 0.9 nmol/l, an increase of 33% over the baseline level of 2.1 ± 0.8 nmol/l, which also was within the normal range. The mean individual change in TT_3 from baseline to peak values was $30\% \pm 10\%$. Peak TT_3 exceeded baseline levels in 12/17 (71%) patients; increases ranged from 5% to 122%. Final (3-month) mean TT_3 levels were essentially unchanged from baseline concentrations (2.2 ± 0.6 nmol/l, $n = 12$ vs 2.1 ± 0.8 nmol/l; $P = NS$). Compared with baseline,

seven patients had decreases of 5–31%, one had unchanged TT_3 levels, and four had increases of 5–46%. The mean individual change in TT_3 from baseline to 3 months was $-4\% \pm 15\%$ ($n = 12$).

Thyroid function – effects on hyper- and hypothyroidism

Within 3 months, rhTSH-augmented, low-dose radioiodine treatment eliminated hyperthyroidism in 10/11 (82%) patients that were subclinically or overtly hyperthyroid at baseline and had an available end-of-study TSH measurement; the remaining patient was subclinically hyperthyroid. Of five patients on thionamides at baseline, three were able to discontinue, and two to reduce dosage of the medication. However, by 3 months after therapy, three patients developed clinical hypothyroidism (endogenous TSH levels of ≥ 4.9 mU/l), and two began thyroid hormone supplementation.

Thyroid volume and tracheal diameter

Final (6-month) mean estimated thyroid volume by CT was significantly reduced from baseline, by 34% (from 170.0 ± 112.8 to 113.3 ± 97.5 ml, $n = 11$; $P < 0.01$). The mean individual thyroid volume reduction during the study was $36\% \pm 22\%$ (data not shown). Thyroid volume decreased in 10 patients by 14.6–70.4% and increased in one patient by 22% (data not shown).

Mean tracheal anteroposterior diameter increased by 14% (from 18.6 ± 4.5 to 21.2 ± 6.9 mm; $P = NS$), while mean lateral diameter increased significantly, by 17% (from 10.9 ± 1.2 to 12.7 ± 1.9 mm; $P < 0.05$). No patient showed a decrease in tracheal diameter.

Table 3 Biochemical response to rhTSH-aided radioiodine treatment.

Patient no.	TSH, mU/l (normal, 0.4–4.0 mU/l)		Total T ₃ , nmol/l (normal, 1.1–2.6 nmol/l)			FT ₄ , pmol/l (normal, 10.0–25.0 pmol/l)		
	Baseline	3-month	Baseline	Peak*	3-month	Baseline	Peak*	3-month
				(% change from baseline)	(% change from baseline)		(% change from baseline)	(% change from baseline)
01	0.3	0.002	3.5	3.5 (0%)	2.9 (–17%)	34.8	41.1 (18%)	28.6 (–18%)
02	1.7	9.9	2.4	2.4 (0%)	NA	16.7	19.7 (18%)	11.0 (–34%)
03	0.9	0.01	1.8	1.8 (0%)	1.8 (0%)	12.2	20.9 (71%)	20.9 (71%)
04	0.1	2.0	2.1	2.6 (24%)	2.0 (–5%)	13.3	20.2 (52%)	7.7 (–42%)
05	0.4	3.9	1.5	2.4 (60%)	1.4 (–7%)	15.5	19.3 (25%)	11.6 (–25%)
06	0.3	4.9	1.8	4.0 (122%)	2.0 (11%)	15.0	41.4 (176%)	8.2 (–45%)
07	0.02	1.2	1.2	2.2 (83%)	NA	14.8	32.6 (120%)	NA
08	0.4	2.8	1.6	2.1 (31%)	NA	12.6	19.2 (52%)	NA
09	0.2	1.3	2.1	2.2 (5%)	1.9 (–10%)	14.0	18.6 (33%)	11.5 (–18%)
10	0.6	2.4	1.7	2.1 (24%)	1.4 (–18%)	14.0	19.3 (38%)	13.4 (–4%)
11	1.1	7.6	1.0	1.5 (50%)	NA	24.1	27.0 (12%)	14.7 (–39%)
12	0.1	1.6	1.9	3.3 (74%)	2.0 (5%)	16.2	20.6 (27%)	12.6 (–22%)
13	0.03	0.7	4.2	4.2 (0%)	2.9 (–31%)	22.4	25.7 (15%)	11.6 (–48%)
14	0.1	0.3	2.3	2.9 (26%)	2.0 (–13%)	20.8	31.6 (52%)	13.6 (–35%)
15	0.1	NA	2.4	2.4 (0%)	NA	17.4	22.1 (27%)	NA
16	0.3	1.5	2.9	4.5 (55%)	3.5 (46%)	15.6	26.2 (68%)	10.6 (–32%)
17	2.0	1.1	2.0	3.4 (70%)	2.3 (15%)	22.6	35.5 (57%)	19.3 (–15%)
Mean±s.d.	0.5±0.6	2.6±2.8	2.1±0.8	2.8±0.9 (33%)	2.2±0.6 (2%)	17.8±5.5	25.9±7.7 (46%)	14.0±5.6 (–21%)

FT₄, free L-thyroxine; NA = not applicable; rhTSH, recombinant human thyroid-stimulating hormone; TSH, thyroid-stimulating hormone; T₃, triiodothyronine.

* Highest of three post-therapy measurements (days 10, 30 and 90).

Figure 3 Serum TSH levels before ('Baseline') and after administration of 0.03 mg rhTSH followed by 30 mCi ^{131}I on day 1. Intervals between measurement points are not shown proportionately.

Symptomatic response

At 6 months, improvement in symptoms, well-being, or both, or decreased need for antihyperthyroid medication was noted in 13 of the 17 (76%) patients, while no patient described symptom worsening, with the exception of three with transient adverse reactions described below (Table 4).

Safety

Low-dose rhTSH itself was generally well tolerated, with no related side effects apparent during the study. rhTSH-aided radioiodine treatment also was well tolerated, but three (18%) patients developed side effects that were possibly or probably related to this modality. Patient no. 12 suffered transient palpitations. Her TSH levels, low at baseline, decreased slightly in the first 10 days after therapy, with a parallel transient increase in FT_4 that did not reach hyperthyroid levels (maximal FT_4 , 20.6 nmol/l). Patient no. 15, a frail, 80-year-old woman, developed fever, malaise and palpitation 1 week after therapy. Her erythrocyte sedimentation rate increased to 25 mm/h. Beta blockers stabilized her pulse at 80 bpm. Sixteen days after radioiodine therapy, she was admitted to a community hospital due to weakness and a mild fever of 37.8 °C that required nursing care. Blood and urine cultures were negative and after 4 days, she was discharged with a tentative diagnosis of post- ^{131}I thyroiditis, although an intercurrent infection could not be ruled out. Although her TSH levels were suppressed, neither her FT_4 nor TT_3 levels exceeded the normal range in any measurement during the study. Patient no. 17 showed transient biochemical hyperthyroidism, accompanied by palpitations that were relieved by a beta blocker. The thyroid function increase became apparent after 30 days and gradually resolved by day 180 – a course that most probably reflects radiation thyroiditis, and not TSH toxicity.

Only one patient (no. 10) had a thyroid volume increase, but remained asymptomatic throughout the

observation period. No patient suffered an acute or symptomatic tracheal obstruction secondary to the therapeutic protocol. Thus, there was no need for adjuvant or prophylactic corticosteroids.

Discussion

Our major aim was to define an rhTSH-augmented radioiodine treatment protocol for MNG that would be safe, effective and simple in aged patients afflicted by comorbidities. The present study demonstrated that intramuscular injection of 0.03 mg rhTSH, followed

Table 4 Symptomatic response to rhTSH-aided radioiodine therapy.

Patient no.	Symptomatic response
1	MTZ treatment 3 months
2	Symptomatic improvement; initiated thyroid replacement therapy
3	MTZ dose reduction from 40 to 10 mg daily; improved well-being
4	Symptomatic improvement, including improved breathing
5	Improved well-being
6	Euthyroid; symptomatic improvement
7	Transient local neck pain
8	Thionamide discontinuation
9	Symptomatic improvement
10	Symptomatic improvement; improved well-being
11	Asymptomatic at baseline, remained so throughout study
12	Palpitation leading to two ER visits but resolving after treatment with propafenone and thionamide discontinuation
13	Thionamide discontinuation
14	Thionamide discontinuation
15	Transient symptomatic thyroiditis leading to hospitalization, beta blocker treatment; eventually euthyroid
16	Symptomatic improvement
17	Transient palpitations successfully treated with beta blocker, transient neck tenderness

ER, emergency room; MTZ, mercaptizol; rhTSH, recombinant human thyroid-stimulating hormone.

24 h later by a fixed 30 mCi activity of ^{131}I , achieves this goal. The 0.03 mg dose of rhTSH itself significantly increased 24-h thyroid RAIU and produced few if any apparent clinical side effects. With 3 months' follow-up, our rhTSH-aided radioiodine treatment regimen eliminated subclinical or overt hyperthyroidism in 82% of evaluable affected patients ($n = 11$), and ameliorated compressive and obstructive symptoms, improved well-being, or reduced or eliminated required medication in 76% of patients. Moreover, the regimen produced hypothyroidism in only 18% of our series, although this must be viewed not as a complication, but rather as a potential natural consequence of radioiodine treatment. Despite the large mean goiter size at baseline, our protocol decreased mean thyroid volume and increased tracheal lateral diameter. At the same time, despite an elderly study population with very prevalent comorbidity, the regimen was associated with clinical side effects in only 18% of individuals. In addition, the regimen could be given on an outpatient basis.

An rhTSH-aided radioiodine treatment regimen similar to ours has been used in MNG by Dutch investigators (12–15). Of interest, their elaborate dosimetric calculations based on test activity RAIU resulted in their using therapeutic activities comparable to ours: 22.8 ± 5.7 mCi (17) or 24.3 ± 5.4 (16) versus 30 mCi. In the Dutch study (15), 0.03 mg rhTSH increased mean 24-h RAIU to a greater degree than it did in our study (145% vs 68%). The difference may be attributable to the markedly greater baseline mean thyroid volume in our study population (170 ± 113 vs 113 ± 33 ml), or to differences in dietary iodine intake. Our regimen also achieved a smaller, if similarly statistically significant, decrease in mean thyroid volume than was seen by the Dutch group: 34% after 6 months (estimated by CT) versus $41\% \pm 12\%$ after 1 year (measured by magnetic resonance imaging) (15). This difference may relate to the larger baseline mean thyroid volume in our study or to the disparate observation times, since further thyroid volume reduction can be expected between 6 months and 1 year, as has been documented with both unstimulated (7, 10) and rhTSH-aided radioiodine treatment (17). Perhaps as a result of the lesser thyroid volume reduction, we noted a markedly lower incidence of hypothyroidism: 18% within 3 months versus 40% within 1 year (15). This finding also may relate to our substantially shorter observation time.

We saw a higher, if still fairly modest, incidence of clinical side effects than did the Dutch investigators: over 6 months, 3/17 (18%) patients with transient hyperthyroid symptoms, mainly palpitation, that spontaneously resolved or responded to beta blockers, versus no clinical adverse events in the day following rhTSH or the 3 months following ^{131}I administration (15). We noted in one patient, and Nieuwlaet *et al.* (15) noted in their entire 0.03 mg rhTSH group, transient thyroid

expansion immediately after radioiodine administration, but, in both studies, the expansion was asymptomatic. The higher incidence of side effects in our patients may be due to their greater mean age (72 ± 8 vs 63 ± 12 years) or their greater prevalence of comorbidity (82% vs none reported).

A Brazilian group also has reported use of a fixed 30 mCi activity in MNG, but with a much higher rhTSH dose (two consecutive daily injections of 0.1 mg) than ours (19). Compared with our study population, their patients ($n = 18$) were somewhat younger (mean age 62 ± 9 years) and had a nearly 60% lower baseline mean goiter size (98 ± 45 vs 170 ± 113 ml) and less than 50% of the baseline 24-h thyroid RAIU ($12.2\% \pm 6.2\%$ vs $25.8\% \pm 10.3\%$). The Brazilian investigators observed a sharper increase in 24-h thyroid RAIU (339% vs 68%). However, they noted a similar reduction in mean thyroid volume at 6 months (39% vs 34%), as did we, probably because post-rhTSH RAIU was similar in the two studies ($53.5\% \pm 10.0\%$ vs $43.4 \pm 8.4\%$). Albino *et al.* (19) found sharper peaks in mean serum FT_4 (146% vs 46% increase from baseline) and serum TT_3 (192% vs 33% increase from baseline) than we did, but this may be due to their inclusion of sampling times before day 10, our first measurement point. After 3 months, mean values for these analytes had changed similarly from baseline in the Brazilian population and our patients (31% vs 21% decrease in mean FT_4 ; 5% vs 2% increase in mean TT_3). The Brazilian study appeared to note a higher rate of adverse reactions to rhTSH-aided radioiodine – mildly painful thyroiditis in 33% and mild thyrotoxicosis, including palpitations, anxiety and asthenia, in 39% of their patients versus clinical symptoms in 18% of ours. Albino *et al.* (19) observed a more than three times higher rate of hypothyroidism than we (65% vs 18%).

A US group also has employed a fixed, rhTSH-aided, radioiodine activity of 30 mCi, but after even higher rhTSH doses (0.3 or 0.9 mg) and, in some cases (6/16), 72 h after rhTSH administration (16). In a population of similar mean age (73 ± 9 years) but with lower baseline mean goiter size (81 ± 25 g) than ours, these investigators attained a similar thyroid volume reduction (30–40%, $n = 15$, estimated by palpation after 3–7 months) but a higher rate of goiter symptom relief (complete remission of compressive/obstructive symptoms in 11/11 patients and improvement or remission of weight loss or atrial fibrillation in 2/2 and 1/2 patients respectively, versus symptom or well-being improvement, or reduction or elimination of required medication in 76% of our patients). An amount of 30 mCi radioiodine stimulated by larger rhTSH doses appeared to be well tolerated in the US study (1/16 patients with increased compressive symptoms, manageable with corticosteroids).

Another team of Brazilian investigators have reported (17) rhTSH-aided radioiodine therapy of very

large MNGs (mean baseline thyroid volume of 281.4 ± 179.2 ml) with a large rhTSH dose (0.45 mg) and a large ^{131}I activity (96.0 ± 40.8 mCi). With 0.45 mg rhTSH, they observed a greater increase in mean 24-h RAIU than we, but not the Dutch investigators (15), did, using 0.03 mg (151% vs 68% vs 145% respectively). However, the Brazilian study demonstrated a 6-month mean thyroid volume reduction (34%) identical to ours and a larger 1-year reduction than that reported by the Dutch investigators (60% vs 41%). Silva *et al.* (17) had the highest incidence of hypothyroidism of the three studies, 65% at 1 year. In addition, in an elderly population with frequent comorbidity, the Brazilian investigators noted local cervical pain, loss of taste and weight loss in the majority of patients (52–65% each), and thyroiditis, esophagitis and sialoadenitis in an appreciable portion (17–24% each).

Given the small populations, frequently nonrandomized study design, and disparate patient characteristics (such as baseline thyroid volumes and dietary iodine intakes), methodologies, and levels of detail in all these reports, any comparison of their results is little more than anecdotal. Nonetheless, our and these other studies initially suggest that low-dose rhTSH stimulation of low-activity radioiodine may be comparably effective to high-dose rhTSH stimulation of low- or high-activity ^{131}I in reducing thyroid volume and alleviating MNG physical or functional symptoms. Low- or high-dose rhTSH stimulation of low-activity radioiodine treatment seems to share relatively good tolerability, although low rhTSH doses may be associated with a smaller incidence of acute thyroid dysfunction. High-dose rhTSH stimulation of high-activity ^{131}I treatment seems to be associated with relatively elevated rates of untoward acute effects. For example, transient hyperthyroidism was noted in all patients 24 h after receiving 0.45 mg rhTSH; on day 7, the mean FT_4 was 30.2 ± 14.6 pmol/l (17). This early increase in TFT points to the rhTSH stimulation rather than the high radioiodine activities as the cause of the hyperthyroidism. However, confirmation or refutation of all the above hypotheses awaits randomized, prospective, comparative trials in patients with comparable characteristics.

Besides its observational nature, our study had several limitations. First, our initial post-treatment TFT measurement was at 10 days after radioiodine and 11 days after rhTSH administration; therefore, it may have missed relevant, shorter-term hormonal effects of these agents. However, in other patients receiving 0.03 mg rhTSH for diagnostic procedures, FT_4 concentrations appreciably exceeded the normal institutional threshold (26.7 pmol/l) in only one of seven cases during the first 48 h after rhTSH, and were normal in all cases at 48 h and 7 days (12), implying that we were unlikely to have missed a major increase in FT_4 levels. Second, our study visit schedule (10, 30, 90

and 180 days after treatment) and the outpatient nature of our protocol might have led to underobservation of clinical adverse reactions, particularly transient events, after rhTSH or radioiodine administration. However, patients were repeatedly instructed to report side effects immediately, and were queried about adverse events throughout the study. Third, the rotation ellipsoid modeling of CT images that we used to estimate thyroid volume is somewhat imprecise, especially in large MNG. However, comparisons of baseline and 6-month volumes were performed on a blinded basis, and the statistical significance of the mean thyroid volume decrease makes gross inaccuracy unlikely. Nonetheless, our main aim was to alleviate the potentially life-threatening metabolic consequences of MNG rather than maximize MNG volume reduction. Because goiter expansion frequently slows during old age, even subtle MNG volume decreases appear likely to provide meaningful clinical benefit in the elderly. Lastly, we did not include measurement of pulmonary or cardiac function, or both, which might be of interest to incorporate in future studies.

In conclusion, our results indicate that use of a single, low dose (0.03 mg) of rhTSH and administration 24 h later of a relatively low, fixed therapeutic activity (30 mCi) of ^{131}I result in a safe, effective and convenient treatment of MNG in elderly patients with large goiters and high prevalence of comorbidities. This protocol merits further evaluation in randomized, prospective studies comparing it to treatment with the same radioiodine activities in the absence of TSH stimulation, or with stimulation by other rhTSH doses.

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