Effect of 30 mCi radioiodine on multinodular goiter previously treated with recombinant human thyroid-stimulating hormone

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Abstract

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Recombinant human thyroid-stimulating hormone (rhTSH) enhances ^{131}I uptake, permitting a decrease in radiation for the treatment of multinodular goiter (MNG). Our objective was to evaluate the safety and efficacy of a single 0.1-mg dose of rhTSH, followed by 30 mCi ^{131}I, in patients with MNG. Seventeen patients (15 females, 59.0 ± 13.1 years), who had never been submitted to ^{131}I therapy, received a single 0.1-mg injection of rhTSH followed by 30 mCi ^{131}I on the next day. Mean basal thyroid volume measured by computed tomography was 106.1 ± 64.4 mL. ^{131}I 24-h uptake, TSH, free-T4, T3, thyroglobulin, anti-thyroid antibodies, and thyroid volume were evaluated at regular intervals of 12 months. Mean ^{131}I 24-h uptake increased from 18.1 ± 9.7 to 49.6 ± 13.4% (P < 0.001), a median 2.6-fold increase (1.2 to 9.2). Peak hormonal levels were 10.86 ± 5.44 mU/L for TSH (a median 15.5-fold increase), 1.80 ± 0.48 ng/dL for free-T4, 204.61 ± 58.37 ng/dL for T3, and a median of 557.0 ng/mL for thyroglobulin. The adverse effects observed were hyperthyroidism (17.6%), painful thyroiditis (29.4%) and hypothyroidism (52.9%). Thyroid volume was reduced by 34.3 ± 14.3% after 6 months (P < 0.001) and by 46.0 ± 14.6% after 1 year (P < 0.001). Treatment of MNG with a single 0.1-mg dose of rhTSH, followed by a fixed amount of radioactivity of ^{131}I, leads to an efficacious decrease in thyroid volume for the majority of the patients, with a moderate incidence of non-serious and readily treatable adverse effects.

Introduction

Multinodular goiter (MNG) is a clinically recognized enlargement of the thyroid gland which is characterized by abnormal growth and structural and/or functional alterations. It is more frequently found among the elderly (particularly women), and its pro-

gression to hyperthyroidism by the development of autonomous activity is a common event (1).

There is no ideal treatment for MNG. Iodine supplementation or levothyroxine (LT-4)-suppressive therapy are disregarded as therapeutic options due to the risks of hyperthyroidism or subclinical hyperthyroidism, especially when higher doses of L-T4 are used (2) and due to the lack of evidence from prospective clinical trials evaluating L-T4 treatment for MNG (3-5). Surgery is the treatment of choice, with many positive aspects, particularly in patients with large MNG. However, complications such as hypoparathyroidism and vocal cord paralysis must be taken into account (6).

The use of radioactive iodine (^{131}I) for MNG treatment has been described in several studies, showing a goiter size reduction ranging from 34 to 49% in the first year (7-14). Most of this reduction occurs during the first three months after ^{131}I therapy (12). However, retrospective studies suggest that the response is directly proportional to the administered ^{131}I activity and inversely related to the initial thyroid volume (14). Also, ^{131}I uptake is commonly low and heterogeneous. Hence, the effective radioactivity is often too high to be administered without hospitalization and isolation.

Recombinant human thyroid-stimulating hormone (rhTSH) has been shown to increase ^{131}I uptake in normal subjects (15) and in patients with MNG (16), and also to provide a more homogenous distribution of radioactive iodine in the gland (17). Taken together, these observations suggest that pretreatment with rhTSH should allow the administration of lower activities of ^{131}I in MNG (18). In a previous study, we showed that the combination of rhTSH given in two 0.1-mg injections prior to a fixed activity of ^{131}I was safe and efficient in achieving thyroid volume (TV) reduction after 6 months (19).

The objective of the present study was to evaluate the efficacy (in terms of TV reduction) of a single dose of 0.1 mg rhTSH, associated with the maximum activity of ^{131}I (30 mCi) allowed for outpatient ^{131}I administration in Brazil. Since large goiters are highly prevalent in Brazil, a high activity was chosen because many patients may need higher radiation activities for an effective TV reduction. By adding rhTSH to the maximum outpatient activity of ^{131}I, we would theoretically enhance TV reduction. We also discuss and compare the results obtained with those of our previous study in which a group with similar characteristics received two doses of rhTSH (19).

Patients and Methods

We evaluated 17 outpatients with MNG (15 females, 2 males, mean age 59.0 ± 13.1 years) who were being followed at the Hospital de Clínicas, Curitiba, PR, Brazil. None of the patients had surgical or TSH-suppressive therapy with LT-4, or ^{131}I treatment. They either had contraindication for surgery or refused a surgical approach, and ^{131}I was considered the treatment of choice. Patients with severe tracheal compression (observed by computed tomography) were excluded from the study, as well as patients with basal 24-h radioactive iodine uptake (RAIU) higher than 30% and patients with malignant nodules.

Prior to treatment, the presence of malignancy was excluded in all patients by ultrasound-guided fine-needle aspiration biopsy of suspicious and/or dominant nodules. TV was measured by a helical computed tomography (Secura, Philips Medical Systems, Andover, MA, USA) with 2.5-mm wide axial sections, followed by multiplane and 3-D reconstruction using the Advantage Work ADW 4.0 workstation (GE Medical Systems, Waukesha, WI, USA).

All patients underwent a ^{131}I scintigraphy and a basal 24-h RAIU test using a rectilinear scanner with a 3-inch thick NaI

crystal (Pho/Dot Scanner, Nuclear-Chicago, Des Plaines, IL, USA) and an uptake measurement device (model 8725, Nuclear-Chicago). These evaluations were performed not more than 3 months prior to treatment with rhTSH. Patients who were taking methimazole (MMI) were advised to stop it 2 weeks before scintigraphy and uptake determination.

Patients were consecutively assigned to the study. All were treated on the same day in October 2003 and followed-up for 1 year.

Basal TV was 106.1 ± 64.4 mL (range: 28 to 270 mL) and RAIU was 18.1 ± 9.7%. At the time of inclusion in the study, 6 patients had subclinical or clinical hyperthyroidism, identified by TSH levels below 0.1 mU/L and free-T4 in the normal or high-normal range. Five of these patients were treated with low doses of MMI (5 to 10 mg/day) for at least 3 months prior to the study, which was stopped 2 weeks prior to ^{131}I therapy. The sixth patient with subclinical hyperthyroidism had never used MMI and was not started on it. Complete physical examination of all patients, including those with subclinical hyperthyroidism, focusing on the heart showed no evidence of cardiac disease.

All subjects were instructed to follow a low-iodine diet (removal of iodized salt and iodine-rich foods) for 2 weeks before the administration of rhTSH.

For treatment, a 0.9 mg vial of rhTSH (Thyrogen®, Genzyme Corp., Cambridge, MA, USA) was reconstituted with 1.2 mL sterile water (provided in the kit) and 1 mL of this solution was added to 9 mL sterile water for injection, providing a 10-mL solution at a 0.1-mg/mL concentration of rhTSH.

One milliliter rhTSH was administered intramuscularly in a single injection of 0.1 mg at day 1 (D1). A ^{131}I activity of 50 µCi (1.85 MBq) was administered, followed by scintigraphy and RAIU on the subsequent day (D2). On that day, a standard therapeutic activity of 1110 MBq (30 mCi) [131]I was administered to all patients. Blood samples were collected on days 1, 2, 3, 5, 10 in order to determine the immediate hormonal changes and at 1, 2, 3, 6, 9, and 12 months for TSH analysis by the micro-particle enzyme immunoassay using AxSYM 3rd generation TSH (Abbott Diagnostics, Abbott Park, IL, USA, reference values 0.49 to 4.67 mU/L, sensitivity 0.006 mU/L, CV ≤20%), free-T4 (micro-particle enzyme immunoassay, AxSYM Free-T4, Abbott Diagnostics, reference values 0.71 to 1.85 ng/dL, sensitivity 0.40 ng/dL, CV ≤10%), T3 (micro-particle enzyme immunoassay, AxSYM T3, Abbott Diagnostics, reference values 79.0 to 149.0 ng/dL, sensitivity 30.0 ng/dL, CV ≤16%), and thyroglobulin (Tg; fluoro-immunoassay, DELFIA Tg kit, Perkin-Elmer/Wallac, Waltham, MA, USA, reference range 2.0 to 70.0 ng/mL, CV ≤4.8%). Serum was collected on days 1, 30, 180, and 360 for the determination of anti-thyroglobulin antibody levels (TgAb; micro-particle enzyme immunoassay, AxSYM anti-Tg, Abbott Diagnostics, reference value <40.0 U/mL, sensitivity 2.0 U/mL, CV ≤15.1%), anti-thyroperoxidase antibody levels (TPOAb; micro-particle enzyme immunoassay, AxSYM anti-TPO, Abbott Diagnostics, reference value <35.0 U/mL, sensitivity 1.0 U/mL, CV ≤12.4%), and thyrotrophin receptor antibodies (TRAb; radioimmunoassay, Kronus, Dana Point, CA, USA, reference value <10.0 U/L). TV reduction was determined by a helical computed tomography scan performed 6 and 12 months after [131]I.

The Ethics Committee of the Hospital de Clínicas, Universidade Federal do Paraná (HC-UFPR), approved the study and all patients signed an informed consent form.

Statistical analysis was performed using the SPSS software version 10.0. Data are reported as means ± SD or as median and range, when not normally distributed (according to the Kolmogorov-Smirnov test). The Mann-Whitney and paired Student *t*-tests were used to analyze differences be-

Table 1. Comparative analysis of patients with clinical/subclinical hyperthyroidism and euthyroidism, before and 24-48 h after recombinant human thyroid-stimulating hormone (rhTSH).

	Euthyroidism	Hyperthyroidism
Basal TSH (mU/L)	0.46 (0.11-2.56)	0.25 (0.01-1.14)
Basal free-T4 (ng/dL)	1.25 ± 0.29	1.07 ± 0.13
Basal T3 (ng/dL)	117.4 (87.4-124.1)	115.5 (86.8-138.7)
TSH (D2) (mU/L)	10.15 (7.15-16.39)	9.54 (0.08-25.96)
Free-T4 (D3) (ng/dL)	1.92 ± 0.46	1.69 ± 0.52
T3 (D2) (ng/dL)	195.8 (145.0-293.9)	173.9 (147.0-342.1)
Basal RAIU (%)	16.1 ± 7.3	19.3 ± 13.4
Post-rhTSH RAIU (%)	51.9 ± 14.5	48.2 ± 12.5
Basal TV (mL)	107.3 ± 56.4	108.5 ± 83.18
Post-rhTSH TV (mL)	61.4 ± 56.4	55.5 ± 42.8
TV reduction after 12 months (%)	45.4 ± 12.4	49.9 ± 18.9

Data are reported as mean ± SD and median (minimum-maximum). TSH = thyroid-stimulating hormone; T4 = thyroxine; T3 = triiodothyronine; D2, D3 = day 2 (24 h after rhTSH) and day 3 (48 h after rhTSH), respectively; RAIU = [131]I 24-h uptake; TV = thyroid volume. There were no statistical differences between groups (Mann-Whitney test where distribution is non-normal and paired Student t-test where distribution is normal).

tween groups, as appropriate. Pearson's correlation coefficient was used to determine the correlation between variables. The time effect was analyzed by the paired Student t-test. Two-sided tests were used and P < 0.05 was considered to be significant.

Results

Six months after treatment, mean TV was reduced from 106.1 ± 64.4 to 73.0 ± 52.0 mL, a mean reduction of 34.3 ± 14.3% (P < 0.001). After 12 months, mean volume was 58.2 ± 41.2 mL, a mean decrease of 46.0 ± 14.6% compared to baseline volume (P < 0.001). There was an additional and significant reduction between the 6th and the 12th month (P = 0.01), but most of the total reduction was obtained during the first 6 months (74%). Before treatment, patients

Table 2. Basal and post-treatment evaluation of 17 patients with multinodular goiter on an iodine-restricted diet treated with 0.1 mg recombinant human thyroid-stimulating hormone (rhTSH) plus 30 mCi [131]I.

Patient	Age (years)	Gender	MMI	PT	HT	TSH (D1)	Pre-rhTSH 24-h [131]I (%)	Post-rhTSH 24-h [131]I (%)	Basal thyroid volume (mL)	Effective activity (µCi/g)	Reduction after 6 months (%)	Reduction after 12 months (%)
1	66	F	No	No	No	0.32	12.7	49.0	150.0	98.0	20.0	46.7
2§	70	F	Yes	No	Yes	0.25	25.6	60.7	45.0	404.7	51.1	57.8
3§	45	F	No	Yes	No	0.94	16.4	24.2	28.0	259.3	17.8	35.7
4§	74	M	Yes	Yes	No	1.14	23.0	54.5	57.0	286.8	64.9	80.7
5	73	F	Yes	No	No	0.07	29.5	62.0	147.0	126.5	42.2	59.1
6	66	F	No	No	Yes	0.01	12.5	51.2	110.0	139.6	31.8	39.1
7	49	F	No	No	No	0.54	12.5	39.4	110.0	107.5	25.4	18.2
8§,§§	26	F	No	Yes	Yes	0.74	16.7	35.8	28.0	383.6	50.0	57.1
9	58	F	No	Yes	No	0.46	21.8	54.8	220.0	74.7	22.7	29.5
10	58	F	No	No	No	0.78	6.5	60.1	90.0	200.3	36.7	57.8
11	37	F	Yes	No	No	0.24	20.3	75.2	120.0	188.0	10.0	33.3
12§	70	F	No	Yes	No	0.11	17.8	47.9	93.0	154.5	36.5	51.6
13§	57	M	No	No	No	0.32	15.0	60.5	116.0	156.5	48.2	56.9
14	67	F	Yes	No	No	0.65	46.8	56.9	270.0	63.2	25.9	48.1
15§	64	F	No	No	No	2.56	12.6	34.0	60.0	170.0	40.0	41.7
16§	61	F	No	No	No	0.13	9.6	48.1	95.0	151.9	37.9	50.5
17§	63	F	No	No	No	1.29	7.8	29.5	65.0	136.2	21.5	35.4
Mean	59.0					0.62	18.1	49.6	106.1	182.4	34.3	46.0
± SD	±13.1					±0.63	±9.7	±13.4	±64.4	±98.5	±14.3	±14.6
Median						0.46	16.4	52.8	95.0	154.5	36.5	48.1
(range)						(0.01-2.56)	(6.5-46.8)	(24.2-75.2)	(28.0-270.0)	(63.2-404.7)	(10.0-64.9)	(18.2-80.7)
% Yes			29.4%	29.4%	17.6%							

MMI = methimazole before rhTSH + [131]I; PT = painful thyroiditis; HT = symptoms of hyperthyroidism after rhTSH + [131]I; TSH(D1) = thyroid-stimulating hormone on day 1; § = hypothyroidism after 12 months; §§ = patient with moderate painful thyroiditis, treated with prednisone.

were divided into two groups, i.e., euthyroidism and subclinical/clinical hyperthyroidism. Although no statistically significant data could be obtained from this classification due to the low power of the test performed (power <0.800, with $\alpha = 0.050$), the tendency to a lack of difference between groups can be observed in Table 1. Overall TV changes are shown in Table 2.

After rhTSH administration, RAIU increased from 18.1 ± 9.7 to $49.6 \pm 13.4\%$ (P < 0.001). The ratio between post- and pre-rhTSH RAIU (RR) was calculated to indicate the fold increase in uptake in response to rhTSH. Median RR was 2.6 (1.2 to 9.2). There was an inverse correlation between RR and the pre-rhTSH [131]I 24-h uptake (r = -0.613, P = 0.009), indicating that patients with lower basal uptake values achieved higher RR values. Also, there was a positive correlation between RR and peak TSH (r = 0.538; P = 0.032). The scintigraphic pattern changed from heterogeneous to a diffuse homogenous uptake after rhTSH administration in all patients.

Effective activity of radiation was defined as the fixed ^{131}I activity of 1110 MBq (30 mCi) divided by the basal thyroid mass and corrected for post-rhTSH uptake. Median effective activity was 154.5 μCi/g (63.2-404.7 μCi/g), and was not correlated with TV reduction after 12 months (r = 0.473; P = 0.055; Figure 1). Also, TV reduction after 12 months did not correlate with post-rhTSH uptake (r = 0.305; P = 0.233). Mean TSH levels increased from 0.62 ± 0.62 mU/L (median: 0.46; range: 0.01 to 2.56 mU/L) at D1 to 10.86 ± 5.44 mU/L (median: 9.97; range 0.08 to 23.52 mU/L) at D2 (P < 0.001). After peaking, TSH started to decline to levels below the normal range, reaching a nadir on day 30 (median 0.01; 0.01 to 1.76 mU/L). By the 2nd month, 52.9% of patients (N = 9) still had TSH levels below the normal range and 4 patients (23.5%) developed clinical or subclinical hypothyroidism. These patients were initiated on LT-4 treatment.

The incidence of hypothyroidism was 41.2% by the 3rd month, 47.0% by the 6th month, and 52.9% by the 12th month.

Free-T4 increased from 1.16 ± 0.24 ng/dL at D1 to 1.80 ± 0.48 ng/dL at D3 (48 h after rhTSH; P < 0.001). Mean free-T4 levels remained within the normal range in all evaluations. Six patients had free-T4 levels higher than 1.9 ng/dL on D3 (mean 2.41 ± 0.23 ng/dL). Basal T3 levels were 110.09 ± 15.07 ng/dL, increasing to 204.61 ± 58.37 ng/dL at D2 (P < 0.001). After D5, mean T3 levels returned to normal. Values with concomitant positive TgAb titers were excluded from the analysis of Tg levels due to the possibility of interference in the assay (particularly when Tg levels were normal). Tg rose from median basal levels of 78.5 ng/mL (19.8 to 453.0 ng/mL) to a peak of 557.0 ng/mL (196.0 to 1450.0 ng/mL; P < 0.001) on day 5. By the 6th and 12th months, Tg levels returned to values similar to basal (median 165.0 and 55.5 ng/mL, respectively; P = 0.164).

Four patients (23.5%) had positive basal titers of TgAb (none had TSH below 0.1 mU/L, and 1 patient had TSH between 0.1
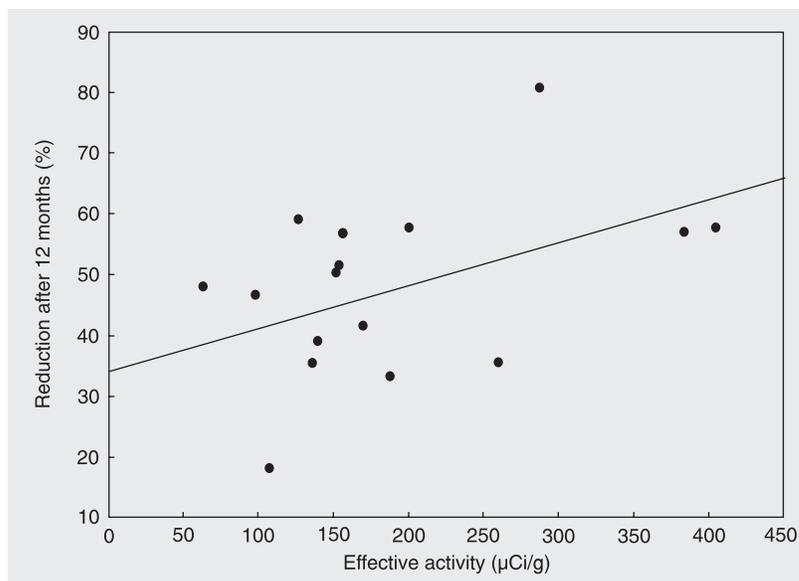

Figure 1. Correlation between thyroid volume reduction after 12 months and effective administered activity (r = 0.473; P = 0.055).

and 0.4 mU/L at D1). This number increased to 9 patients at 6 months but returned to 4 patients with TgAb-positive titers at the last evaluation (2 of them had negative basal TgAb titers). Basal TPOAb titers were positive in 3 patients (17.6%; 1 of them had TSH below 0.4 mU/L and the others had normal TSH). By the 6th month, another patient developed positive TPOAb titers, which remained positive by the 12th month. No patients had positive TRAb titers before treatment. After 12 months, 5 of them developed detectable TRAb (three of them had TSH between 0.1 and 0.4 mU/L and the others had normal TSH). One patient who developed positive TRAb titers had positive TPOAb titers at D1.

One patient (a 71-year-old female) had basal levels of TSH of 0.03 mU/L, basal levels of free-T4 of 1.52 ng/dL and basal levels of T3 of 118.8 ng/dL. She was started on 10 mg MMI 3 months prior to treatment, her basal RAIU was 7% (measured 2 weeks after interruption of MMI, without an iodine-restricted diet) and she had positive TRAb titers (56 U/L), but Graves' ophthalmopathy was absent (as per clinical assessment). At first, she was not considered to have autoimmune hyperthyroidism (positive TRAb and low TSH were present, but she presented a MNG with very low basal RAIU and further evidence of autoimmune hyperthyroidism was lacking), and she was included in the treatment. However, after 6 months, she showed suppressed levels of TSH (0.002 mU/L) and high levels of free-T4 (3.21 ng/dL). A diagnosis of autoimmune hyperthyroidism was made and a new activity of 30 mCi ^{131}I was administered to her (without rhTSH), with resolution of her hyperthyroidism after 2 months. This patient was excluded from all analyses.

Three patients (17.6%) developed at least one sign or symptom of hyperthyroidism (such as palpitation, increased heart rate, insomnia, anxiety, and asthenia) between D5 and D10. Development of signs or symptoms of hyperthyroidism was not related to a previous history of subclinical hyperthyroidism since none of these patients had basal levels of TSH lower than 0.1 mU/L, although rhTSH may induce hyperthyroidism in patients with subclinical hyperthyroidism. Two of these patients were started on propranolol at doses ranging from 80 to 120 mg daily, with prompt improvement in response to therapy. The other patient was already taking atenolol, 50 mg/day, and the dosage was doubled. ß-blockers were discontinued in these first 2 patients and the dosage was halved back to its former dose in the patient already on atenolol at D10. Three patients who did not show signs or symptoms of hyperthyroidism were already taking ß-blockers as part of their anti-hypertensive treatment. Five patients (29.4%) showed symptoms of painful radiation-related thyroiditis starting at least 1 week after ^{131}I administration, characterized by cervical pain, which resolved with non-steroid anti-inflammatory drugs. One patient did not respond and was started on prednisone, 20 mg/day for 5 days, with resolution of thyroiditis. None of our patients developed serious side effects such as respiratory or compressive symptoms.

Dissatisfaction regarding final TV was observed in 1 patient (final TV of 67 mL, with a 39.0% reduction). New therapeutic approaches were offered to this patient, including a new trial of rhTSH and ^{131}I, but she refused them.

Discussion

The efficacy of treatment of MNG with ^{131}I alone is usually hampered by the low and irregular ^{131}I uptake, requiring the administration of higher ^{131}I activities in order to enhance the therapeutic response (1). rhTSH is fairly safe and has the ability to increase ^{131}I uptake, thus being useful in the follow-up of differentiated thyroid cancer (20,21). In patients with MNG, it has been shown

that rhTSH increases ^{131}I uptake, changing the ^{131}I uptake pattern from heterogeneous to homogeneous (17,18). Also, rhTSH transiently increases thyroid hormone levels and TV (22). Another recent study suggested that rhTSH could influence the ^{131}I kinetics, hindering the decrease in thyroid uptake and enhancing the absorbed activity (23).

In the present study, the combination of rhTSH and a fixed activity of 1110 MBq (30 mCi) of ^{131}I resulted in a mean TV reduction of 34.3 ± 14.3% after 6 months and 46.0 ± 14.3% after 1 year. An earlier image evaluation could be valuable since there may be a transient increase of the gland within the 1st month (22). TV reduction was more efficient when compared to studies which used the same radiation activity without rhTSH (24), but was similar to that reported in studies in which higher ^{131}I activities were administered, without rhTSH (7-14). In the present study, effectiveness regarding TV reduction after 6 months was comparable to that found in our previous study (19), in which two doses of 0.1 mg rhTSH were given (reduction of 39.3 ± 19.5% in the previous study, P = 0.390). Data for the 1-year follow-up have not been published yet, but still no statistical difference has been found (reduction of 47.5 ± 21.7% in the previous study, P = 0.890). It is important to say that the patient characteristics in the two studies were similar regarding age, basal TV, basal ^{131}I uptake, and basal thyroid function, permitting a consistent comparison between studies.

We chose to use the highest ^{131}I activity allowed by Brazilian regulations due to the high basal TV and to the low pre-rhTSH RAIU, in order to achieve proper TV reduction in most of the patients. Also, we used a fixed instead of a calculated activity of ^{131}I because some patients would have to receive a much higher activity and would have to be admitted to the hospital. Previous studies using lower ^{131}I activities without rhTSH have shown effective TV reduction. How-

ever, treatments had to be repeated two or more times in some patients (12,13). In the present study, 94.1% of the patients achieved a TV reduction of at least 25%. The protocol was convenient and easy to perform. Its costs may be substantially lower since it decreases the likelihood of a second treatment being needed. Also, it can be done in an outpatient setting, avoiding the need for hospitalization.

In a prolonged follow-up of 4 years, additional volume reduction was similar for patients treated with rhTSH plus ^{131}I or ^{131}I alone (25), despite the fact that, in the first year, more pronounced reduction was seen in the group treated with rhTSH + [131]I (26). In a recent study, a similar volume reduction was achieved with 30 mCi of ^{131}I and a dose of rhTSH three times higher than used in the present study (27). In a randomized, placebo-controlled study, effective reduction was increased by rhTSH (28). These studies have provided important data about the treatment of MNG with rhTSH plus [131]I. However, it is not possible to compare these studies due to the different amounts of rhTSH used and ^{131}I administered, and also due to the different characteristics of the patients.

We could not find any correlation of TV reduction with post-rhTSH ^{131}I uptake, area under the curve of TSH, basal TV, or effective activity of [131]I. However, the level of significance was very close to 0.05 for the effective activity (P = 0.055). Even though no correlations could be shown, TV reduction was satisfactory. This probably happened because all variables are interdependent and influence TV reduction together. The effects of LT-4 on TV could be taken into consideration, but, as shown by previous studies (29), we do not believe that LT-4 could have influenced TV reduction.

After rhTSH, mean RAIU was 49.6 ± 13.4%, also comparable to the uptake found in our previous study (53.5 ± 11.0%; 19). However, this increase in uptake could be underestimated because tracer activity was

given a few minutes after rhTSH, while sodium/iodine symporter was not yet completely stimulated (30). Moreover, the iodine-restricted diet could have contributed, in part, to the increased uptake after rhTSH. Anti-thyroid drug use could be another confounder because its discontinuation two weeks before radioiodine could be insufficient to obtain maximum ^{131}I uptake. However, RAIU, TV and thyroid hormone levels could not be analyzed in two separate groups (patients with normal thyroid function and patients with subclinical hyperthyroidism) because the power of the test was too low.

There was a lower increase in TSH, free-T4 and T3 levels in the present study compared to our previous one (19). In fact, mean free-T4 levels increased 56.5 ± 29.3% and reached a normal-high peak, in contrast to the free-T4 levels of our previous study, which reached a 146% increase and remained high until the first-month evaluation (19). Peak levels of T3 were 87.0 ± 49.0% higher than basal in the present study, as opposed to a 202% increase in T3 when two doses of rhTSH were given (19). These differences are reflected in the occurrence of hyperthyroidism, which was higher (39%) in patients who received two doses of rhTSH (19), *vs* 17.6% in the present study. Even though Tg levels rose considerably, peak level was lower than the mean level of 1838.5 ng/dL found in our previous study (19). This could be attributed to less stimulation with rhTSH and a milder destruction of the parenchyma by ^{131}I when a single dose of rhTSH is given. After 12 months, Tg reached levels similar to baseline, reflecting the absence of stimulation by rhTSH.

TgAb titers returned to baseline values by the 12th month, reflecting destruction of thyroid tissue. We could not define a pattern in the change in TPOAb titers. TRAb titers increased considerably, a fact related to the effect of radiation and more common among patients with positive TPOAb titers (31). Rubio et al. (32) have shown that positive

TPOAb and TRAb titers may occur after ^{131}I, regardless of rhTSH. Moreover, most TRAb have blocking effects on TSH receptors.

The incidence of adverse effects was considerably high, but all of them were mild to moderate and limited to the first 10 days of therapy. All patients with signs and symptoms of hyperthyroidism were treated with 80 mg (if mild) or 120 mg (if moderate) of propranolol. Treatment was limited to the 10th day, with complete resolution. Patients who were already taking ß-blockers as antihypertensive therapy did not develop signs or symptoms of hyperthyroidism, suggesting that ß-blockers could be administered prior to treatment to prevent patients from developing hyperthyroidism. Also, all patients who developed symptoms of painful thyroiditis (characterized by cervical pain) were treated with a non-steroidal anti-inflammatory drug (if the symptom was mild). One patient did not respond to the anti-inflammatory drug and was treated with 20 mg prednisone for 5 days, with important clinical improvement. The incidence of positive TgAb titers was higher among patients who developed symptoms of thyroiditis (60.0 *vs* 8.3%), suggesting that positive titers of TgAb may increase the risk for radiation thyroiditis. The incidence of painful thyroiditis in the present study (29.4%) was similar to that of the comparison study (33.3%), in which two doses of rhTSH were used (19).

The incidence of hypothyroidism was 47.0% after 6 months and 52.9% after 1 year. After 2 years, all patients in the present study were submitted to thyroid function tests, and the incidence of hypothyroidism remained 52.9%. This indicates that even though the incidence of hypothyroidism was high, it did not increase after one year. All patients who developed hypothyroidism had positive TPOAb titers. Also, patients who developed hypothyroidism had lower basal TV than patients who remained euthyroid at

the end of the study (60 *vs* 155 mL, P < 0.003). These findings suggest that positive TPOAb titers and the presence of smaller goiters may increase the risk for the development of hypothyroidism. After one year, the incidence of hypothyroidism was 52.9% in patients who received one dose of rhTSH compared to 70.6% in patients who received two doses of rhTSH (19; Paz-Filho GJ, Mesa-Junior CO, Carvalho GA, Graf H, unpublished data).

In this uncontrolled therapeutic study, we evaluated the efficacy and safety of treatment with one dose of rhTSH, and compared our data to those obtained in a previously published study (19), which had many simi-larities, except for the use of two doses of rhTSH. Although the present study did not have a placebo group, we conclude that treatment of MNG with a single 0.1-mg dose of rhTSH plus 1110 MBq (30 mCi) [131]I is as efficient as two doses on consecutive days in reducing TV in MNG, with a lower incidence of hyperthyroidism.

Acknowledgments

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