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Recombinant human TSH increases the efficacy of a fixed activity of radioiodine for treatment of multinodular goitre

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SUMMARY

Context: High doses of ^{131}I are usually needed in the treatment of multinodular goitre (MNG) for effective thyroid volume (TV) reduction. Recombinant human thyroid-stimulating hormone (rhTSH) is an adjuvant to enhance ^{131}I uptake, allowing a decrease in radiation activity and enhancing ^{131}I efficacy. **Objective:** To evaluate whether rhTSH increases the efficacy of a fixed activity of ^{131}I for the treatment of MNG. **Design:** Two-year, observational, placebo-controlled study. **Setting:** Patients received 0.1 mg rhTSH (A), 0.005 mg rhTSH (B) or placebo (C). A fixed activity of 1.11 GBq of ^{131}I was administered 24 h after rhTSH or placebo. **Patients:** A total of 28 outpatients (26 females and two males) with MNG. **Measurements:** TSH, free T4, T3, thyroglobulin (Tg) and TV. **Results:** Basal radioactive iodine uptake and TV values were comparable among all groups. After rhTSH or placebo, peak levels of TSH, free T4, T3 and Tg were higher in A than in B or in C ($p < 0.05$). Hyperthyroidism was observed in A ($n = 2$), B ($n = 6$) and C ($n = 4$). Thyroid enlargement was reported in A ($n = 3$) and B ($n = 6$). After 24 months, 10 patients developed hypothyroidism (four in A, three in B and three in C). TV reduction was similar between A and B (37.2 ± 25.5% vs. 39.3 ± 27.9%, $p = 0.88$), but different from the non-significant reduction in C (15.3 ± 28.3%, $p = 0.08$). **Conclusions:** Followed by 1.11 GBq, a very low dose of 0.005 mg rhTSH was equally safe and effective as 0.1 mg rhTSH. Both doses increased the efficacy of radioiodine. Adverse events were mild, transient and readily treatable.

What's known

Recombinant Human thyroid-stimulating hormone (TSH) is a safe and useful adjuvant for the treatment of multinodular goitre, by allowing a decrease in the administered activity of radioiodine that is needed for effective results or by increasing radioiodine efficacy compared to treatment with radioiodine alone. Ongoing trials remain to confirm these affirmations and to determine the optimal doses of rhTSH and radioiodine.

What's new

Our study adds further evidence that recombinant human TSH increases the efficacy of radioiodine for the reduction of the volume of multinodular goitres. The lowest dose of recombinant human TSH ever used in a clinical trial (0.005 mg) is equally effective as 0.1 mg for the treatment of large goitres, as an adjuvant to radioiodine.

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Disclosures

Paz-Filho GJ is a consultant for Genzyme do Brasil.

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Introduction

Multinodular goitre (MNG) is defined as a nodular enlargement of thyroid gland, not associated with hyperthyroidism and which does not result from an autoimmune or inflammatory process (1). There is no optimal treatment for MNG and treatment decisions must be individualised. There are four main treatment options for MNG: monitoring without treatment, thyroidectomy, levothyroxine suppression (disregarded as a therapeutic option because of its adverse effects) and radioactive iodine (2).

Radioiodine, in the form of the isotope ^{131}I, has been used for the treatment of MNG with many positive results. By using ultrasound (US), computed tomography (CT) or magnetic resonance imaging, studies have shown that ^{131}I therapy in patients with MNG results in a mean reduction in thyroid volume (TV) of approximately 40% after 1 year and of 50–60% after 2–5 years (3–10). For effective results, the amount of ^{131}I administered depends on the TV and on the radioactive iodine uptake (RAIU) at baseline. However, patients with non-toxic nodular goitre usually have low RAIU because of low or low-normal levels of serum TSH. For reasons of low RAIU, the administration of high doses of ^{131}I is usually required, which leads to considerable irradiation of extra-thyroidal organs and tissues (11). Therefore, it is of interest to explore strategies to enhance RAIU in these patients.

Recombinant human TSH (rhTSH) has become available for diagnostic and therapeutic use in patients with differentiated thyroid cancer (12–14). Huysmans et al. (15) demonstrated that a single low dose of rhTSH increases considerably the RAIU in patients with MNG. These authors have also shown

that rhTSH treatment not only increases RAIU, but also leads to a more homogeneous distribution of ^{131}I within the gland. Therefore, rhTSH stimulates uptake in previous relatively 'cold' areas (16). Taken together, these studies suggest that rhTSH pretreatment may improve the efficacy of treatment with ^{131}I for volume reduction in MNG, especially in patients with a low baseline serum TSH level (5,17). Different doses of rhTSH used in patients with MNG reveal a similar pattern, with a clear dose–response effect between rhTSH and thyroid biomarkers. Higher responses in the serum levels of TSH, free T4 (fT4), T3 and thyroglobulin (Tg) were observed with higher doses of rhTSH (18–21). The optimal dose of rhTSH prior to ^{131}I therapy remains to be settled and the intended positive effect on thyroid RAIU and later TV reduction in MNG must be balanced against undesirable consequences, such as hyperthyroidism and goitre swelling (22).

In search of the safest and most effective doses of rhTSH and ^{131}I, different combinations of rhSTH and ^{131}I have been evaluated in clinical trials (19,21,23–27). In this observational study, we aimed to determine the efficacy (in terms of TV reduction) and safety of a fixed activity of 1.11 GBq of ^{131}I, associated with placebo, 0.005 or 0.1 mg of rhTSH. The highest outpatient activity of ^{131}I allowed by the Brazilian government was chosen to achieve maximum TV reduction in most of the patients. The lowest dose of rhTSH ever evaluated in the literature was compared to placebo and to a dose used in several studies (0.1 mg).

Patients and methods

Patients

Twenty-eight outpatients (26 females, two males, median age of 61 years) with diagnosis of MNG (either by palpation or US), were recruited to participate in the study. All patients were being followed at the Hospital de Clínicas, of Curitiba, Brazil. None of the patients had previous surgery, TSH-suppressive therapy with T4, or radioactive iodine treatment. All patients were candidates for ^{131}I therapy. At recruitment, none of the patients had serious medical conditions and all of them had subclinical hyperthyroidism (which was treated with methimazole) or were euthyroid.

Methods

Prior to treatment, all patients underwent an US-guided fine-needle aspiration biopsy of suspicious and/or dominant nodules to exclude malignancy. ^{131}I scintigraphy and basal 24-h RAIU were performed, using a rectilinear scanner with a 3-inch thick NaI crystal (Pho/Dot scanner, Nuclear Chicago, Des Plaines, IL) and an uptake measurement device (model 8725, Nuclear Chicago). TV was measured using helical CT (Secura; Philips Medical Systems, Andover, MA) with 2.5 mm wide axial sections, with posterior multiplane and 3D reconstruction using the Advantage Work ADW 4.3 workstation (GE Medical Systems, Waukesha, WI). To determine TV, the entire thyroid gland was delimitated and the 'volume rendering' option was selected in the software. After automatically performing transverse sections, the software provided TV.

Basal RAIU and thyroid scintigraphy were performed 1–3 months prior to the treatment with rhTSH, without diet iodine restriction and with interruption of methimazole (MMI) (when in use) 2 weeks before the evaluation. After the measurement of basal RAIU, MMI was reinitiated and interrupted again 2 weeks before treatment. Basal levels of thyroid hormones reflected clinical status on the day rhTSH was administered, 2 weeks without MMI. Except for basal fT4, data were similar among groups and are summarised in Table 1.

Three treatment protocols were designed and patients were randomly assigned to group A: 0.1 mg rhTSH, group B: 0.005 mg rhTSH or group C: placebo.

For treatment, a 0.9 mg vial of rhTSH (Thyrogen®; Genzyme Corp., Cambridge, MA) was diluted in 9.0 ml of sterile water for injection, which resulted in a 0.1 mg/ml dilution. Patients in group A ($n = 9$) received a single intramuscular dose of 1.0 ml (0.1 mg) of rhTSH on day 1 (D1). Patients in group B ($n = 9$) received 0.005 mg of rhTSH, also in a single intramuscular injection on D1. This dose was obtained by the dilution of 0.1 mg of rhTSH in 19 ml of phosphate-buffered saline (PBS), which resulted in a 0.005 mg/ml solution of rhTSH. A single intramuscular injection of 1.0 ml of saline solution was given to patients in group C ($n = 10$).

On D2, a standard therapeutic activity of 1.11 GBq of ^{131}I was given to all patients. Blood samples were collected on days 1, 2, 3, 5, 10 and 1, 2, 3, 6, 9 and 12 months for TSH (Abbott Diagnostics, Abbott Park, IL, reference values 0.49–4.67 mU/l, sensitivity 0.006 mU/l, CV ≤ 20%), fT_4 (micro-particle enzyme immunoassay, AxSYM Free T4, Abbott Diagnostics, reference values 0.71–1.85 ng/dl, sensitivity 0.40 ng/dl, CV ≤ 10%), T3 (micro-particle enzyme immunoassay, AxSYM T3, Abbott Diagnostics, reference values 79.0–149.0 ng/dl, sensitivity 30.0 ng/dl, CV ≤ 16%), and Tg (fluoro-immunoassay, DELFIA Tg kit; Perkin-Elmer/Wallac, Waltham, MA, reference range 2.0–70.0 ng/ml, CV ≤ 4.8%). TV reduction was

Table 1 Baseline characteristics

	0.1 mg rhTSH (A)	0.005 mg rhTSH (B)	Placebo (C)	p-Value (ANOVA)
Men (*n*)	0	0	2	
Women (*n*)	9	9	8	
Age (years)	61 (49–73)	60 (48–73)	62 (45–86)	0.89
BMI (kg/m^2)	28.9 (22–40)	29.9 (25–35)	29.6 (23–35)	0.83
Methimazole (*n*)	3	4	6	0.51
Thyroid volume (ml)	153.2 ± 74.4	103.1 ± 79.7	145.1 ± 78.3	0.14
	168.0 (47.0–300.0)	90.0 (30.0–300.0)	112.5 (43.0–270.0)	
RAIU (%)	19.7 ± 11.5	14.2 ± 5.4	11.9 ± 8.2	0.12
Urinary iodine (μg/24 h)	229.2 (81–504)	231.5 (115–351)	205.5 (74–1388)	0.86
TSH (mUI/l)	0.39 (0.002–1.44)	0.21 (0.003–3.0)	0.33 (0.02–1.14)	0.93
Free T4 (ng/dl)	1.5 (1.1–2.6)*	1.4 (1.0–2.1)	1.2 (0.8–1.7)	0.04
T3 (ng/dl)	144 (117–270)	139 (121–173)	127 (76–251)	0.38
Thyroglobulin (ng/ml)	171.0 (0.6–1890.0)	103.0 (7.6–520.0)	126.5 (29.0–3630.0)	0.66

*Levels of free T4 were significantly higher in group A; values given as median (minimum–maximum) or mean ± SD. rhTSH, recombinant human TSH; BMI, body mass index; RAIU, radioactive iodine uptake.

evaluated through helical CT scan performed 6, 12 and 24 months after ^{131}I.

Recruitment began in February 2004 and all patients were treated on the same day in November 2004. All patients were followed-up for 24 months. Patients were instructed to maintain their normal diet during all times. A 24-h urine sample was obtained from all patients on D1 to evaluate urinary iodine concentration.

The Ethical Committee of the Hospital de Clinicas of the Universidade Federal do Paraná approved the study and all patients signed an informed consent form.

Results were expressed as mean ± SD or median (range). The Kolmogorov–Smirnov test was used to test normality of distributions. Groups were compared by ANOVA or the Kruskal–Wallis test. The time effect was analysed by the Student paired *t*-test or Wilcoxon test, as appropriate. Pearson or Spearman correlation coefficients, as appropriate, were used to assess the relation between variables. One-way ANOVA with repeated measures was used to evaluate the volume reduction after 6, 12 and 24 months. Two-sided tests were used with $p < 0.05$ considered significant. Calculations were performed using SPSS software, Version 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

At recruitment, none of the patients had overt hyperthyroidism. Fourteen patients had subclinical hyperthyroidism and only one participant from group A had never received MMI. Among all patients who received MMI, treatment was given for at least 3 months prior to the study and was stopped twice (2 weeks prior to RAIU and 2 weeks before ^{131}I therapy). Dose ranged from 5 to 10 mg qd. After stopping MMI, some patients developed overt hyperthyroidism, with fT4 levels above the reference range. However, only clinical observation was undertaken, without the need for MMI. Two patients in group A, who were in use of MMI, were also taking propranolol 80–120 mg qd. This drug was maintained during all times. Baseline characteristics are summarised in Table 1.

Thyroid volume reduction

Basal TV, measured by helical CT scan, was similar among all groups ($p = 0.24$) and decreased 6, 12 and 24 months after the therapy with rhTSH. After 6, 12 and 24 months, TV was significantly different among the three groups. Table 2 presents the individual and mean volumes during the study. At the 6th month, TV reduced from 153.2 ± 74.4 to 117.7 ± 70.5 ml (27.3 ± 17.9%) in group A ($p < 0.001$) and from 103.1 ± 79.7 to 84.6 ± 81.4 ml (24.6 ± 14.8%) in group B ($p = 0.003$). When groups A and B were compared, they presented similar results ($p = 0.75$). Group C did not experience significant reduction in TV (from 145.1 ± 78.3 to 145.4 ± 91.1 ml, 5.5 ± 20.4%; $p = 0.96$).

After 12 months, the mean TV decreased significantly from 153.2 ± 74.4 to 111.4 ± 72.8 ml ($p < 0.001$) in group A and from 103.1 ± 79.7 to 77.7 ± 81.2 ml in group B ($p < 0.001$). In group C,

Table 2 Individual thyroid volumes before and after treatment with rhTSH or placebo plus ^{131}I

Group	Patient	Basal TV (ml)	TV 6 months (ml)	TV 12 months (ml)	TV 24 months (ml)
A	1	168	160	145	100
	2	300	260	260	247
	3	164	90	87	*
	4	180	145	140	160
	5	47	18	12	11
	6	90	75	81	80
	7	180	116	97	95
	8	80	55	36	25
	9	170	140	145	128
	Mean ± SD	153.2 ± 74.4	117.7 ± 70.5	111.4 ± 72.8	105.8 ± 75.3
B	1	90	70	60	78
	2	89	63	49	46
	3	300	290	280	280
	4	96	75	91	80
	5	95	58	32	25
	6	120	100	89	*
	7	78	68	70	*
	8	30	14	09	08
	9	30	23	19	17
	Mean ± SD	103.1 ± 79.7	84.6 ± 81.4	77.7 ± 81.2	76.3 ± 94.2
C	1	115	92	†	†
	2	230	250	240	*
	3	200	178	168	170
	4	43	27	18	14
	5	93	120	100	110
	6	270	280	270	287
	7	220	260	245	*
	8	60	47	45	41
	9	110	110	93	91
	10	110	90	90	110
	Mean ± SD	145.1 ± 78.3	145.4 ± 91.1	141 ± 92.8	117.6 ± 90.2

*Patients lost to follow-up; †Death due to unrelated ischemic cerebral stroke. rhTSH, recombinant human TSH; RAIU, radioactive iodine uptake; TV, thyroid volume.

TV did not change (from 145.1 ± 78.3 to 141 ± 92.8 ml; $p = 0.27$). The observed average reductions were 32.9 ± 23.2% in group A, 33.2 ± 24.2% in group B and 12.7 ± 21.5% in group C.

After 24 months, when compared to the TV at baseline, the mean TV decreased from 153.2 ± 74.4 to 105.8 ± 75.3 ml in group A ($p < 0.001$) and from 103.1 ± 79.7 to 76.3 ± 94.2 ml in group B ($p = 0.001$). No significant changes were seen in group C (from 145.1 ± 78.3 to 117.6 ± 90.2 ml; $p = 0.08$). Reduction was similar in groups A and B (37.2 ± 25.5% vs. 39.3 ± 27.9% respectively, $p = 0.88$). In group C, TV reduction was not significant after 24 months (15.3 ± 28.3%). Regression analysis showed no correlations between TV reduction and urinary iodine levels in groups A ($r = 0.546$, $p = 0.161$), B ($r = 0.234$, $p = 0.613$) or C ($r = -0.598$, $p = 0.157$). Similarly, no correlations were observed between TV reduction at the 24th month and TV at baseline for groups A ($r = 0.433$, $p = 0.24$), B ($r = 0.58$, $p = 0.101$) or C ($r = 0.54$, $p = 0.114$). There was a positive correlation between volume reduction and the TSH area under the curve only in group A ($r = 0.75$, $p = 0.02$).

Thyroid function and thyroglobulin responses

Serum TSH concentration increased significantly compared to baseline values after administration of either 0.1 mg ($p = 0.007$) or 0.005 mg rhTSH ($p = 0.015$; Figure 1) with a peak 24 h after rhTSH injection in both groups (mean TSH of 8.0 ± 3.4 mU/l and median TSH of 6.6 with a range of 3.7–13.6 mU/l in group A; mean TSH of

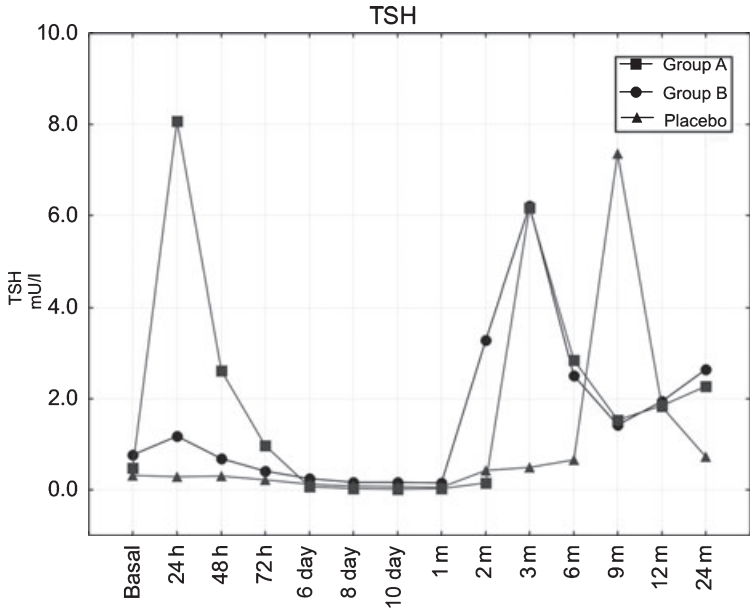

Figure 1 Mean serum TSH concentrations in groups A and B increased significantly compared to baseline values after administration of either 0.005 or 0.1 mg recombinant human TSH (rhTSH) for both groups, and peaked 24 h after rhTSH injection. In the placebo group, there was no significant change in the serum TSH levels after the treatment

1.2 ± 1.1 mU/l and median TSH of 0.7 with a range of 0.4–3.9 mU/l in group B). There was a significant difference between peak TSH in groups A and B ($p = 0.0005$). In the placebo group C, there were no significant changes in serum TSH levels ($p = 0.500$). Serum TSH concentrations remained elevated for 72 h after rhTSH administration in group A. Whenever TSH levels began to rise after the first month of treatment (> 4.0 mU/l), levothyroxine was initiated.

Maximal serum fT4 concentrations were reached 1–2 days after rhTSH administration in group A, with an increase from 1.6 ± 0.4 to 2.5 ± 0.7 ng/dl ($p = 0.01$). Non-significant and similar fT4 changes were observed in groups B (from 1.38 to 1.44 ng/dl; $p = 0.67$) and C (from 1.14 to 1.23 ng/dl; $p = 0.09$). Serum T3 concentrations peaked 48 h after treatment in groups A and B, with a higher increase in group A (from 167.6 ± 52.4 to 321.1 ± 72.7 ng/dl; $p = 0.007$) vs. group B (from 144.3 ± 19.8 to 181.8 ± 42.2 ng/dl; $p = 0.01$). Non-significant changes in T3 were observed in group C (from 138.2 ± 53.2 to 150.43 ± 32.5 ng/dl; $p = 0.138$). Serum fT4 and T3 concentrations remained significantly elevated for as long as 30 days (fT4) and 8 days (T3) in group A. Triiodothyronine and fT4 returned to baseline levels after 1 and 2 months, respectively. Changes in fT4 and T3 are illustrated in Figure 2.

Median Tg was 171 ng/ml at baseline in group A and peaked 72 h after treatment (508.0 ng/ml; range 2.0–2300.0 ng/ml; $p = 0.01$). There were no significant increases in median Tg levels in group B and group C from baseline (103 and 126.5 ng/ml respectively) to the median peak levels (142.0 ng/ml, $p = 0.08$; and 166.0 ng/ml, $p = 0.57$, respectively for B and C).

Adverse events

Adverse events were mild, self-limited and the treatment was well-tolerated. Twelve patients (43%) developed a few symptoms of hyperthyroidism such as palpitation, anxiety, headache or asthenia (two in group A, six in group B and four in group C) without clinical significance. Only one patient warranted the use of a β-blocker in a low dose, with prompt improvement in symptoms. Without treatment, symptoms of hyperthyroidism were resolved within 2–5 days after onset. Nine patients (32%) referred enlargement of the thyroid without compressive symptoms, and/or moderate cervical pain, which resolved with non-steroidal anti-inflammatory drugs (three in group A and six in group B). The overall incidence of hypothyroidism was 14.2% by the 3rd month, 21.4% by the 6th month and 25.9% by the 12th month. After 24 months, 10 patients (45%) developed hypothyroidism (four in group A, three in group B and three in group C). Subclinical hyperthyroidism was reversed in 4/4 patients in group A, 4/4 patients in group B and 6/6 patients in group C. In the placebo group, a 71-year-old female died 8 months after treatment of complications of an unrelated ischemic cerebral stroke. Prior to the

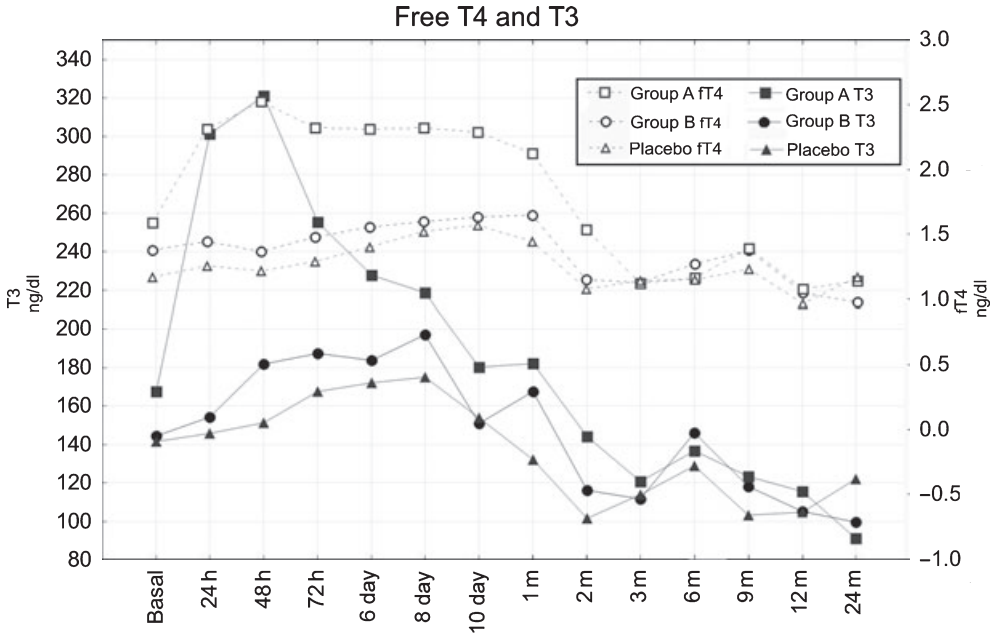

Figure 2 Mean serum-free T4 concentrations peaked 1–2 days after recombinant human TSH (rhTSH) or placebo administration. Serum-free T4 concentrations after the treatment were similar in groups B and C. Serum T3 concentrations peaked 48 h after the treatment in all groups

treatment, she had subclinical hyperthyroidism, but her thyroid function normalised after ^{131}I.

Discussion

In this observational study, we showed that rhTSH increases effectiveness of ^{131}I. A very low dose of rhTSH (0.005 mg) plus 1.11 GBq of ^{131}I was more effective than placebo and as effective as a low dose (0.1 mg), in terms of TV reduction in patients with MNG. Pretreatment with rhTSH prior to ^{131}I therapy led to a significant goitre volume reduction, which was more efficient than the reduction observed in studies that used the same fixed activity (28) or calculated amounts of ^{131}I (3–10), without rhTSH. In the latter studies, calculated doses of ^{131}I were given, which resulted in a large dose range, as opposed to our study, where a fixed activity was used. In discordance with the three randomised studies with a placebo group (23,25,27), we did not observe significant changes in TV in the placebo-treated group. In this group, response was diverse and some of the patients experienced increase in TV during the follow-up. Among the rhTSH-treated patients, no comparisons could be made between those randomised studies and our own, since doses of rhTSH were higher and activities of ^{131}I, calculated. In our study, TV at baseline was similar for all groups (by ANOVA, $p = 0.14$). Regression analysis presented further evidence that the initial TV did not correlate with TV reduction.

Radioiodine-131 is an effective treatment for patients with MNG. This therapeutic approach, however, presents variable responses and a relatively high frequency of treatment failure, mainly if the goitre is very large and if TSH is suppressed (29). A higher reduction of TV in groups pretreated with rhTSH is most likely because of enhanced uptake of the radioactive iodine and to prolonged permanency of the radioisotope within the gland thyroid (16). In our study, we used the maximum activity of ^{131}I that is permitted for outpatient treatment by the Brazilian regulatory agencies. That approach allowed us to maximise the number of patients with significant TV reduction in all groups. By administering a fixed activity of ^{131}I, we realised that a few patients in group C did not receive optimal treatment. However, it would not be logistically feasible to increase the administered activity beyond the one that is allowed for outpatient treatment.

In our study, patients did not follow an iodine-restricted diet prior to the treatment. Levels of urinary iodine indicated that the patients were under an iodine-sufficient diet. However, urinary iodine levels were very heterogeneous, with some patients excreting more than 500 μg/day. The absence of an iodine-restricted diet may have contributed to the heterogeneous response in all groups and to the absence of significant increase in RAIU. Nevertheless,

we could find no correlations between TV reduction and levels of urinary iodine, partially because of this large range of iodine levels. In spite of the lack of correlations, we recommend that all patients undergo a low-iodine diet for 2 weeks prior to thyroid scanning, as well as 2 weeks prior to the radioiodine therapy.

In this study, mean fT4 levels remained unchanged in groups B and C, in contrast with the levels in group A. In that group, higher levels of fT4 were observed and remained high until the first-month evaluation. Thyroid hormones were elevated for a more prolonged period than in other studies. This difference, however, was not reflected in an increase in hyperthyroidism symptoms, which were similar among groups A and B. Even though Tg levels rose in both groups, this was much more evident in group A, possibly because of a higher degree of stimulation with rhTSH. After 6 months, Tg levels reached baseline levels, reflecting TV reduction and the absence of the stimulatory effects of rhTSH.

Incidence of thyroiditis was also similar in both groups, which is an indirect evidence that both were under the same effect of thyroid destruction by radiation. The incidence of hypothyroidism was similar in all groups, and was not correlated with the TV reduction, as one would expect. It is possible that, in our patients, the activity of radioiodine was sufficient to induce hypothyroidism, but not to reduce TV in a similar degree. Subclinical hyperthyroidism was reversed in all patients by 1.11 GBq of ^{131}I, regardless of the use of rhTSH.

To obtain more homogenous results, we should have excluded patients with extremely large goitres, high RAIU and high urinary iodine levels. Moreover, post-rhTSH RAIU measurement should have been undertaken at least 24 h after rhTSH. However, this would not have changed our outcomes, as the study was designed to test whether rhTSH increases ^{131}I efficacy, not whether rhTSH allows a reduction in ^{131}I activity. Patients with toxic and non-toxic goitre were included, because we designed this study to be applicable in the clinical setting, where most of the patients with MNG have areas of autonomy and low levels of TSH.

In this observational study, we compared the treatment efficacy and safety in three groups of patients with MNG receiving 0.1 mg of rhTSH, 0.005 mg of rhTSH or placebo 24 h before 1.11 GBq of ^{131}I. We conclude that a very low dose of rhTSH increases the efficacy of ^{131}I. When followed by a standard ambulatory dose of 1.11 GBq of ^{131}I, the low dose 0.005 mg rhTSH is as effective as a higher dose in reducing TV in MNG and is accompanied by mild, transient and readily treatable adverse events. Ongoing trials remain to confirm these findings and to determine the optimal doses of rhTSH and radioiodine.

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Author contributions

Elisangela Cubas: Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics and Data collection. **Gilberto Paz-Filho:** Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics and Data collection. **Marcia Olandoski:** Data analysis/interpretation, Approval of article and Statistics. **Carlos Goedert**: Concept/design, Data analysis/interpretation, Approval of article and Data collection. **Luiz Woellner:** Concept/design, Approval of article and Data collection. **Gisah Carvalho**: Concept/design, Critical revision of article, Approval of article and Data collection. **Hans Graf:** Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article and Statistics.

References

1 Krohn K, Fuhrer D, Bayer Y et al. Molecular pathogenesis of euthyroid and toxic multinodular goiter. *Endocr Rev* 2005; **26**: 504–24.
2 Samuels MH. Editorial: evaluation and treatment of sporadic nontoxic goiter – some answers and more questions. *J Clin Endocrinol Metab* 2001; **86**: 994–7.
3 Bonnema SJ, Bertelsen H, Mortensen J et al. 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* 1999; **84**: 3636–41.
4 de Klerk JM, van Isselt JW, van Dijk A et al. Iodine-131 therapy in sporadic nontoxic goiter. *J Nucl Med* 1997; **38**: 372–6.
5 Hegedus L, Hansen BM, Knudsen N, Hansen JM. Reduction of size of thyroid with radioactive iodine in multinodular non-toxic goitre. *BMJ* 1988; **297**: 661–2.
6 Huysmans DA, Hermus AR, Corstens FH et al. Large, compressive goiters treated with radioiodine. *Ann Intern Med* 1994; **121**: 757–62.
7 Le Moli R, Wesche MF, Tiel-Van Buul MM, Wiersinga WM. Determinants of longterm outcome of radioiodine therapy of sporadic non-toxic goitre. *Clin Endocrinol (Oxf)* 1999; **50**: 783–9.

8 Nygaard B, Hegedus L, Gervil M et al. Radioiodine treatment of multinodular non-toxic goitre. *BMJ* 1993; **307**: 828–32.
9 Wesche MF, Tiel VBMM, Lips P et al. A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. *J Clin Endocrinol Metab* 2001; **86**: 998–1005.
10 Wesche MF, Tiel-v-Buul MM, Smits NJ, Wiersinga WM. Reduction in goiter size by 131I therapy in patients with non-toxic multinodular goiter. *Eur J Endocrinol* 1995; **132**: 86–7.
11 Huysmans DA, Buijs WC, van de Ven MT et al. Dosimetry and risk estimates of radioiodine therapy for large, multinodular goiters. *J Nucl Med* 1996; **37**: 2072–9.
12 Ramirez L, Braverman LE, White B, Emerson CH. Recombinant human thyrotropin is a potent stimulator of thyroid function in normal subjects. *J Clin Endocrinol Metab* 1997; **82**: 2836–9.
13 Robbins RJ, Voelker E, Wang W et al. Compassionate use of recombinant human thyrotropin to facilitate radioiodine therapy: case report and review of literature. *Endocr Pract* 2000; **6**: 460–4.
14 Ladenson PW, Ewertz ME, Dickey RA. Practical application of recombinant thyrotropin testing in clinical practice. *Endocr Pract* 2001; **7**: 195–201.
15 Huysmans DA, Nieuwlaat WA, Erdtsieck RJ et al. Administration of a single low dose of recombinant human thyrotropin significantly enhances thyroid radioiodide uptake in nontoxic nodular goiter. *J Clin Endocrinol Metab* 2000; **85**: 3592–6.
16 Nieuwlaat WA, Hermus AR, Sivro-Prndelj F et al. Pretreatment with recombinant human TSH changes the regional distribution of radioiodine on thyroid scintigrams of nodular goiters. *J Clin Endocrinol Metab* 2001; **86**: 5330–6.
17 Silva MNC, Rubio IGS, Romao R et al. Administration of a single dose of recombinant human thyrotrophin enhances the efficacy of radioiodine treatment of large compressive multinodular goitres. *Clin Endocrinol* 2004; **60**: 300–8.
18 Torres MST, Ramirez L, Simkin PH et al. 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* 2001; **86**: 1660–4.
19 Albino CC, Mesa CO Jr, Olandoski M et al. Recombinant human thyrotropin as adjuvant in the treatment of multinodular goiters with radioiodine. *J Clin Endocrinol Metab* 2005; **90**: 2775–80.
20 Paz-Filho G, Mesa C, Carvalho G et al. Recombinant human TSH associated with radioiodine does not have further effects on thyroid volume and function after two years. *Clin Endocrinol (Oxf)* 2007; **69**: 345–6.
21 Paz-Filho GJ, Mesa-Junior CO, Olandoski M et al. Effect of 30 mCi radioiodine on multinodular goiter previously treated with recombinant human thyroid-stimulating hormone. *Braz J Med Biol Res* 2007; **40**: 1661–70.
22 Nielsen VE, Bonnema SJ, Hegedus L. The effects of recombinant human thyrotropin, in normal subjects and patients with goitre. *Clin Endocrinol* 2004; **61**: 655–63.
23 Bonnema SJ, Nielsen VE, Boel-Jorgensen H et al. Improvement of goiter volume reduction after 0.3 mg recombinant human thyrotropin-stimulated radioiodine therapy in patients with a very large goiter: a double-blinded, randomized trial. *J Clin Endocrinol Metab* 2007; **92**: 3424–8.
24 Cohen O, Ilany J, Hoffman C et al. Low-dose recombinant human thyrotropin-aided radioiodine treatment of large, multinodular goiters in elderly patients. *Eur J Endocrinol* 2006; **154**: 243–52.
25 Nielsen VE, Bonnema SJ, Boel-Jorgensen H et al. Stimulation with 0.3-mg recombinant human thyrotropin prior to iodine 131 therapy to improve the size reduction of benign nontoxic nodular goiter: a prospective randomized double-blind trial. *Arch Intern Med* 2006; **166**: 1476–82.
26 Nieuwlaat WA, Huysmans DA, van den Bosch HC et al. 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* 2003; **88**: 3121–9.
27 Silva MN, Rubio IG, Romao R et al. Administration of a single dose of recombinant human thyrotrophin enhances the efficacy of radioiodine treatment of large compressive multinodular goitres. *Clin Endocrinol (Oxf)* 2004; **60**: 300–8.
28 Zelmanovitz FZT, Zelmanovitz W. Radioactive iodine 131 treatment of nontoxic multinodular goiter with ambulatory doses. *Endocr J (Japan)* 2000; **47** (Suppl.): 144 (Program of the 12th Thyroid Congress, Kyoto, Japan).
29 Pedersen-Bjergaard U, Kirkegaard C. Serum TSH and the response to radioiodine treatment of toxic multinodular goitre. *Eur J Endocrinol* 1997; **137**: 365–9.

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