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USEFULNESS OF RECOMBINANT HUMAN TSH AIDED RADIOIODINE DOSES ADMINISTERED IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

FABIAN PITOIA[1], ELIAS EL TAMER[2], DANIEL B. SCHERE[3], MARIANO PASSERIEU[1], OSCAR D. BRUNO[1], HUGO NIEPOMNISZCZE[1]

[1]División Endocrinología; [2]Centro de Medicina Nuclear-UBA-CNEA, Hospital de Clínicas José de San Martín, Facultad de Medicina, Universidad de Buenos Aires; [3]Laboratorio de Medicina Nuclear, Buenos Aires

Abstract The published studies confirming the safety and efficacy of rhTSH for diagnostic purposes have led to an increased interest in its use for preparation for radioiodine (RI) dose administration in patients with recurrent or persistent differentiated thyroid carcinoma (DTC). In order to establish the efficacy of RI therapy after rhTSH, we have reviewed 39 rhTSH-aided radioiodine treatment in a series of 28 DTC patients. Patients were divided into two groups: GI (n=17), with previous thyroid bed uptake and undetectable thyroglobulin (Tg) levels under levothyroxine treatment and GII (n=11), with proven metastatic local or distant disease. Median follow-up after the first rhTSH-aided radioiodine treatment was 32 ± 13 months (range 8 to 54 months). Sixteen patients (94%) in GI were rendered disease free and one patient was shown to have persistent disease. In GII, the post therapy whole body scan showed pathological uptakes in all cases: in four patients in lungs, in four in mediastinum and in three in lateral neck. In two patients with mediastinum uptake, Tg levels were undetectable after rhTSH. In the follow-up, two patients with lateral neck uptake were rendered disease free, four patients died (three due to thyroid cancer) and five out of the remaining patients have persistent disease. In conclusion, rhTSH aided therapy was helpful to eliminate normal thyroid bed remnants in 16/17 (94%) patients (GI). rhTSH stimulated Tg was undetectable in two patients with mediastinal metastasis. We believe that rhTSH is a good alternative to levothyroxine withdrawal for the treatment of DTC with radioactive iodine, increasing the quality of life in these patients. Caution should be recommended in the follow-up of unselected DTC patients only with stimulated Tg levels.

Key words: cancer, thyroid, recombinant TSH, treatment, rhTSH

Resumen ***Administración de dosis terapéuticas de radioyodo luego de TSH recombinante en pacientes con carcinoma diferenciado de tiroides.*** Los estudios publicados que confirman la seguridad y eficacia de la TSH recombinante (rhTSH) llevaron a un incremento en el interés para su uso como adyuvante terapéutico en el CDT (ablación o tratamiento de enfermedad metastática). Para evaluar la efectividad de la administración de dosis terapéuticas de RI luego de la administración de rhTSH, realizamos un análisis retrospectivo en 28 pacientes con CDT que recibieron 39 dosis de RI. Los pacientes se dividieron en 2 grupos: GI (n=17) pacientes con captación en el lecho tiroideo y niveles indetectables de tiroglobulina (Tg) bajo tratamiento supresivo con levotiroxina y GII (n=11), pacientes con enfermedad metastática local o a distancia, previamente comprobada. El seguimiento promedio luego de la primera dosis de RI fue de 32 ± 13 meses (rango 8 a 54 meses). Dieciseis pacientes (94%) del GI fueron considerados libres de enfermedad y un paciente presentó una persistencia local. En el GII, las captaciones patológicas fueron: en 4 pacientes en pulmones; en 4 en mediastino y en 3 a nivel lateral cervical. Dos pacientes con captaciones mediastinales presentaron niveles indetectables de Tg. En el seguimiento, dos pacientes con captaciones latero-cervicales se consideraron libres de enfermedad, cuatro pacientes murieron (tres debido al CDT avanzado) y cinco de los restantes tienen enfermedad persistente. En conclusión, la terapia con RI luego de rhTSH fue útil para ablacionar remanentes normales en el GI. Los niveles de Tg estimulados con rhTSH fueron indetectables en dos pacientes con metástasis mediastinales. El uso de rhTSH parece ser una alternativa válida frente a la suspensión de la terapia hormonal en el tratamiento de pacientes con CDT, incrementando la calidad de vida de estos pacientes.

Palabras clave: cáncer, tiroides, TSH recombinante, tratamiento, rhTSH

Differentiated thyroid carcinoma has an excellent prognosis after the initial treatment, which usually includes near-total thyroidectomy and radioiodine ablation of post-surgical thyroid remnants[1]. The incidence of differentiated thyroid cancer (DTC) has increased in many places around the world over the past three decades, but this has been associated with a significant decrease in DTC mortality rates in some countries. While the best 10-year DTC survival rates are about 90%, long-term relapse rates

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Postal address: Dr. Fabián Pitoia, Esmeralda 961 PB "J", 1007 Buenos Aires, Argentina.
Fax: (54-11) 4312-9891 e-mail: fpitoia@intramed.net

remain high, in the order of 20–40%, depending upon the patient's age and tumor stage at the time of the initial treatment[2].

In order to administer a radioiodine dose it is necessary to obtain an adequate ^{131}I uptake in the mestastatic focus. For this aim, a suppressive therapy with thyroid hormone must be withdrawn, during several weeks, to raise endogenous TSH to levels associated with increased iodine uptake by thyroid tissue (greater than 25 mUI/l)[3, 4].

Levothyroxine ($L\text{-}T_4$) withdrawal, however, may be associated with signs and symptoms of severe hypothyroidism that is generally poorly tolerated. In some cases, the hypothyroid status may be fatal in patients with very poor physical conditions, advanced age, and in the presence of large metastatic foci or another concomitant illness (renal failure, heart disease, pituitary disease)[5, 6]. Because of the availability of recombinant human thyrotropin (rhTSH)[7-9], it has been proposed to perform patient follow-up after exogenous TSH stimulation without $L\text{-}T_4$ withdrawal. Recently, it has been suggested that patients with low risk papillary thyroid carcinoma might be followed with rhTSH stimulated thyroglobulin (Tg) alone associated with ultrasonography to establish the disease free status[10, 11]. This procedure avoids adverse effects and discomfort caused by the $L\text{-}T_4$ withdrawal-induced hypothyroidism[5]. These advantages would be even more important if radioiodine treatment could be indicated using rhTSH in all patients with thyroid cancer.

In the period 1997-2004, nearly 30 medical centers worldwide have reported almost 400 patients with DTC who were given rhTSH in preparation for radioiodine ablation of thyroid remnants or treatment for local tumours of metastatic disease. Recently, an excellent review performed by Luster et al.[12] analyzed and summarized the findings reported in the literature.

In this paper we report the results after having previously used rhTSH to administer radioiodine for thyroid remnant ablation and treatment in a series of 28 DTC patients.

Materials and Methods

Patients

A total of 39 radioiodine doses after exogenous TSH stimulation with rhTSH (Thyrogen, Genzyme Transgenics Corp., Cambridge, MA) were performed in 28 patients (24 women and 4 men; median age 58 years old, range 23 to 89 y.o.). All patients had histologically documented papillary thyroid carcinoma with primary diagnosis established between 1984 and 2002. Six out of the 28 patients were in stage IVc by TNM classification, the remaining patients were classified as follows: Stage IVa, n=1; Stage III, n= 3 and Stage I, n= 18. Previous treatments had included: total thyroidectomy in all but one patient who had had a lobectomy; and post-surgical radioiodine ablation in all of them. Patients were divided into 2 groups: GI (n=17), subjects with previous thyroid bed uptake and measurable stimulated Tg levels (between 1.3 and 3 ng/ml) but undetectable under $L\text{-}T_4$ suppresive therapy (≤ 1 ng/ml). These patients were believed to have a "normal" thyroid remnant which had not been completely ablated after the first radioiodine dose; and GII (n=11), patients with proven metastatic local or distant disease.

Some of these patients (2 in GI and 5 in GII) had also undergone previous ^{131}I treatments, beside the post surgical ablative dose (median number of treatments, n=3; range 1 to 8) after conventional $L\text{-}T_4$ withdrawal with a mean cumulative activity of 507 ± 247 mCi (range 200 to 850 mCi)

RhTSH aided therapy was indicated due to the following reasons: advanced disease with poorly physical condition (n=9), previous hypothyroid state intolerance and/or patient denial to receive a new treatment after conventional withdrawal (n=13), depression (n=2), secondary hypothyroidism (n=1) and advanced age with other associated disorders (n=3). The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000. Before treatment, all patients gave a written informed consent.

Methods

Before treatment, baseline serum TSH, T_4, T_3, free T_4, Tg and anti-thyroglobulin antibodies (Tg-Ab) levels were measured in all patients using commercially available kits. All patients were receiving $L\text{-}T_4$ at the moment of the beginning of the protocol.

Under the treatment protocol, 30 days before the radioiodine dose, $L\text{-}T_4$ was changed to T_3 (doses between 20 to 40 µg/day) in all patients[13]. One week before the ^{131}I dose, a low iodine diet was indicated. This diet was continued until two days after the ^{131}I dose.

All patients received an IM dose of 0.9 mg rhTSH on 2 consecutive days followed by an oral administration of ^{131}I on day 3 (Fig. 1) The ^{131}I administered activities ranged from 30 to 300 mCi, adjusted individually based on TNM stage, and presence of metastasis. Fifteen patients of Group I received one radioiodine dose (mean administered activity of 92 ± 41 mCi, range 30 to 150 mCi), one patient received two doses (cumulative activity of ^{131}I=130 mCi) and one subject three doses (cumulative activity of ^{131}I= 250 mCi). In Group II, five patients had one radioiodine dose after rhTSH (mean ^{131}I dose was 230 mCi, range 150 to 300), four received two doses (mean cumulative activity of ^{131}I of 475 mCi, range 350 to 600 mCi) and 2 patients received three ^{131}I doses (both subjects had a mean cumulative activity of 600 mCi). Patients with documented or suspected metastases were treated with glucocorticoids (prednisolone 40 mg/day) for 2 days before and 5 days after the radioiodine dose to prevent tumor

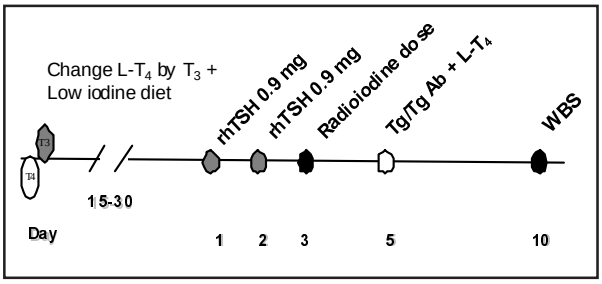

Fig. 1.– Employed protocol in 28 patients who received ^{131}I treatment after the administration of recombinant human TSH (rhTSH). Radioiodine dose was adjusted individually based on patients and tumor characteristics. Levothyroxine ($L\text{-}T_4$) was changed for T_3 between 15 to 30 days prior to the radioiodine dose administration. Tg: Thyroglobuline, Tg-Ab: Thyroglobulin antibodies.

swelling resulting in compression of sensible structures as CNS or spine[14]. Serum Tg and Tg-Ab were measured on day 5 after the first rhTSH injection. T_3 was withdrawn and L-T_4 was restarted on the same day. Whole body scan (WBS) was performed within 5-7 days after radioiodine therapy.

Mean post therapy follow-up was 32 ± 13 months (range 8-54 months). It included regular measurement of serum Tg under L-T_4 treatment and additional WBS/Tg measurements performed after rhTSH administration. Other diagnostic procedures were performed (chest X-ray, neck ultrasonography in all patients, and chest CT in 10 patients).

Results

After rhTSH-aided radioiodine treatment 16/17 (94%) patients of GI were rendered disease free, with negative WBS and undetectable Tg levels. One of these patients with thyroid bed uptake and undetectable Tg levels under L-T4, showed lateral right neck uptake after 150 mCi of ^{131}I, with stimulated Tg levels of 9 ng/ml. An ultrasonography showed pathological lymph nodes. A fine needle aspiration biopsy demonstrated a papillary carcinoma metastasis. The patient was then re-operated on and the pathological examination revealed 4 of 15 lymph nodes with metastatic papillary carcinoma. In 1/17 patients with undetectable Tg levels after rhTSH, a lateral neck uptake was shown to be a false positive uptake caused by a laringocele[15].

In GII, the WBS after the therapeutic dose/s showed pathological uptake/s in all cases (in 4 patients in the lungs; in 4, in the mediastinum; and in the other 3, in the lateral neck). In 2 patients with mediastinum uptake, Tg levels were undetectable after rhTSH administration or after L-T_4 withdrawal performed 6 month previously. A MRI showed no alterations in mediastinum in any of them.

In the follow-up, two patients with lateral neck uptake were rendered disease free, four patients died (3 due to advanced thyroid cancer) and five are still having persistent disease: one patient with nodular lung metastasis increased Tg levels *on* L-T_4 treatment (from 17 ng/ml to 257 ng/ml) one year after 200 mCi ^{131}I administration. One patient with lateral neck uptake stabilized his Tg levels after two radioiodine doses. Mediastinal uptake was observed in the remaining three patients with persistent disease. In one of them the Tg level was undetectable and stabilized persistent disease was observed after two radioiodine doses in the remaining two patients (Table 1).

No adverse events were seen in this cohort of patients. Analysis of serum TSH, performed two days after the first rhTSH injection, showed sharp increases in all patients (mean serum TSH level 117 ± 34 mUI/l, range 90 to 178 mUI/l).

Discussion

In published experiences to date, rhTSH-aided ablation has shown efficacy in a majority of cases when radioiodine doses were equal or superior to 30 mCi and especially when they were higher than 100 mCi[16-21]. Recently, Pacini et al.[22] presented the first prospective multicentric randomized study on ablation comparing results after the administration of 100 mCi in two situations: after rhTSH

TABLE 1.– *Baseline thyroglobuline (Tg) levels under L-T_4 treatment and outcome for patients with metastatic disease undergoing radioiodine treatment after rhTSH. Each Tg measurement beyond baseline indicates the control after each radioiodine dose*

Patient	Gender	Age (years)	Baseline Tg levels (ng/ml)	Tg after the first RI dose (ng/ml)	Tg after the second RI dose (ng/ml)	Tg after the third RI dose (ng/ml)	Metastatic site (WBS uptake)	Overall outcome
1	F	73	187	90	210	1287	Lungs	Death
2	F	82	17	20			Lungs	PD
3	F	64	180	120			Brain/Lungs	Death
4	F	49	< 1*	< 1	< 1	< 1	Lungs	Death
5	F	81	5	< 1			Lateral neck	DF
6	F	79	4	3.5	3.2		Lateral neck	PD
7	F	73	5.6	3.1	< 1		Lateral neck	DF
8	M	61	90	50	70		Mediatinum	PD
9	F	45	< 1	< 1			Mediastinum	PD
10	M	89	< 1	< 1			Mediastinum	Death
11	M	72	6	5	5.2		Mediastinum	PD

Tg: thyroglobulin ; RI: radioiodine; WBS: whole body scan; F: female; M: male; PD: persistent disease; DF: disease free.
** Undetectable Tg levels due to high Tg-Ab titles.*
Tg levels were measured under L-T4 suppressive therapy baseline and three months after each RI dose.

or after thyroid hormone withdrawal. Preliminary results showed that rates of ablation were similar in both situations.

However, Pacini et al.[19] have shown that the 30-mCi standard dose of ^{131}I for post-surgical ablation of thyroid remnants was less effective when patients were prepared with recombinant human TSH (54%) instead of thyroid hormone withdrawal (84%). They have attributed such a finding to an accelerated iodine clearence in the euthyroid patients, leading to the observation that their initial dose rate delivered to the residues was lower, as well as the 24-h radioiodine uptake. We think that the main reason for these findings could have a different explanation. Perhaps, the stable iodine content present in L-T_4 could decrease radioiodine thyroid cell uptake. By using T_3 instead of L-T_4, as we did, the competition with radioiodine would considerably decrease, leading to an increased uptake by the thyroid remnants and, perhaps, permitting a higher activity of the radioiodine dose, especially when using doses lower than 100 mCi[13]. Recently, Barbaro et al.[20] administered an ablative dose of 30 mCi and compared two similar groups of patients. Following the same rationale, the group that received ablation after rhTSH, discontinued L-T_4 from the day before the first rhTSH injection until the day after the radioiodine dose administration. Mean urinary iodine in overnight urine collected between the last rhTSH injection and the time of administration of ^{131}I, was significantly lower than that observed in 16 other patients receiving rhTSH for diagnostic purposes that continued with L-T_4 treatment. At 1-year, follow-up rates of successful remnant ablation, showed by rhTSH-stimulated negative WBS were similar in both groups, a substantial difference when compared with Pacini's study[19].

On the other hand, longer residence times in thyroid remnants and reduced blood doses were observed performing dosimetric studies after rhTSH-aided radioiodine administration[23]. These results would suggest that the activity needed to ablate the remnant is not likely to be higher than that required in the hypothyroid state.

In publications to date, rhTSH has been used for a variety of reasons to aid radioiodine treatment[24-45]. The majority of patients were treated under the Genzyme's compassionate use programme. In many of these cases rhTSH aided radioiodine therapy was indicated in elderly patients with bulky, widespread or end-stage thyroid cancer. The analysis of published outcomes of rhTSH-aided treatment showed that around 65% of patients presented clinical benefit from this modality, that is, complete or partial remission or disease stabilization[12].

The efficacy of the rhTSH aided radioiodine treatment in our GII is very difficult to establish in most of the cases due to the advanced DTC status at the time performed. However, two patients with lateral neck uptake were considered disease free. Although all of our patients had a diagnosis of papillary thyroid cancer, the use of rhTSH-aided treatment could be extensive to all patients with differentiated thyroid cancer, including those with the follicular type.

The percentage of patients with low or undetectable Tg levels and positive WBS usually found in the different patient series is low[46-49]. Interestingly, two of our patients of Group II presented mediastinal uptake after a 200 mCi ^{131}I radioiodine dose associated with undetectable Tg levels.

Metastatic spread detected only by WBS with lacking of Tg rises might be explained by several reasons such as the small size of tumor, unable to release detectable amounts of Tg[50], or loss of the ability of secreting Tg with preserved capability of ^{131}I trapping[48,50,51]. Another explanation of low levels of Tg in patients with persistent disease identified by WBS can be found in structural changes of Tg . The alterations of Tg structure would occur due to a reduced iodine content[52] and due to different quality of amino acidic residues and monosaccharides composition of Tg in papillary thyroid carcinomas in comparison with normal Tg[53].

Although rhTSH stimulated Tg is increasingly being recommended as the gold-standard in the follow-up of patients with DTC, it is important to bear in mind that this protocol should be only indicated in those low risk papillary thyroid cancer patients, as previously suggested[10,11].

In conclusion, in this uncontrolled restrospective analysis, rhTSH aided therapy was well tolerated in all patients. It was helpful to eliminate normal thyroid bed remnants in most of our patients of Group I. The efficacy in patients with metastatic disease is very difficult to establish in most of our cases due to the advanced DTC status at the time of this experience. However, it is well known that this kind of patients generally have the same outcome after radioiodine treatment, following the traditional L-T_4 withdrawal. We believe that rhTSH is a good alternative to L-T_4 withdrawal for the treatment of DTC with radioactive iodine. Caution is recommended when follow-up is performed only with stimulated Tg levels in unselected patients.

Conflict of interests: Fabián Pitoia is an external clinical advisor for Genzyme Corporation.

References

1. Schlumberger MJ. Papillary and follicular thyroid carcinoma. *N Engl J Med* 1998; 338: 297–306.
2. Mazzaferri E, Massoll N. Management of papillary and follicular (differentiated) thyroid cancer: new paradigms using recombinant human thyrotropin. *Endocr Relat Cancer* 2002; 9: 227-47.
3. Goldman JM, Line BR, Aamodt RL, Robbins J. Influence of triiodothyronine withdrawal time on ^{131}I uptake postthyroidectomy for thyroid cancer. *J Clin Endocrinol Metab* 1980; 50: 734–9.
4. Schlumberger M, Charbord P, Fragu P, et al. Rela-

tionship between thyrotropin stimulation and radioiodine uptake in lung metastases of differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 1983; 57: 148–51.
5. Dow KH, Ferrel BR, Anello C. Quality of life changes in patients with thyroid cancer after withdrawal of thyroid hormone therapy. *Thyroid* 1997; 7: 613-9.
6. Goldberg LD, Ditchek NT. Thyroid carcinoma with spinal cord compression. *JAMA* 1981; 245: 953-4.
7. Meier CA, Braverman LE, Ebner SA, et al. Diagnostic use of recombinant human thyrotropin in patients with thyroid carcinoma (Phase I/II Study). *J Clin Endocrinol Metab* 1994; 78: 188-96.
8. Ladenson PW, Braverman LE, Mazzaferri EL, et al. Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. *N Engl J Med* 1997; 337: 888-95.
9. Haugen BR, Pacini F, Reiners C, et al. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J Clin Endocrinol Metab* 1999; 84: 3877-85.
10. Mazzaferri EL, Robbins RJ, Spencer CA, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. *J Clin Endocrinol Metab* 2003; 88: 1433-41.
11. Schlumberger M, Berg G, Cohen O, et al. Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. *Eur J Endocrinol* 2004; 150: 105-12.
12. Luster M, Lippi F, Jarzab B, et al. rhTSH-aided radioiodine ablation and treatment of differentiated thyroid carcinoma: a comprehensive review. *Endocr Relat Cancer* 2005;12: 49-64.
13. Pitoia F, Degrossi OJ, Niepomniszcze H. Why should the radioiodine dose be different in patients with differentiated thyroid carcinoma prepared with recombinant human TSH? *Eur J Nucl Med Mol Imaging* 2004; 31: 924; author reply: 924-5.
14. Pitoia F, Niepomniszcze H. Tumor growth after recombinant human TSH. *Clin Endocrinol (Oxf)* 2002; 57: 301.
15. Niepomniszcze H, Schere D. How to distinguish between radioiodine accumulation in a laryngocele from a radioiodine-concentrating thyroid remnant after thyroidectomy for papillary carcinoma. *Thyroid* 2004; 14: 867-8.
16. Robbins RJ, Tuttle RM, Sonenberg M, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin. *Thyroid* 2001; 11: 865-9.
17. Robbins RJ, Larson SM, Sinha N, et al. A retrospective review of the effectiveness of recombinant human TSH as preparation for radioiodine thyroid remnant ablation [brief communication]. *J Nucl Med* 2002; 43: 1482-8.
18. Berg G, Lindstedt G, Suurküla M, Jansson S. Radioiodine ablation and therapy in differentiated thyroid cancer under stimulation with recombinant human thyroid-stimulating hormone (rhTSH). *J Endocrinol Invest* 2002; 25: 44-52.
19. Pacini F, Molinaro E, Castagna MG, et al. Ablation of thyroid residues with 30 mCi 131I: a comparison in thyroid cancer patients prepared with recombinant human TSH or thyroid hormone withdrawal. *J Clin Endocrinol Metab* 2002; 87: 4063-8.
20. Barbaro D, Boni G, Meucci G, et al. Radioiodine treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: effectiveness for postsurgical remnants ablation and possible role of iodine content in L-thyroxine in the outcome of ablation. *J Clin Endocrinol Metab* 2003; 88: 4110-5.
21. Kovatcheva RD, Hadjieva TD, Kirilov GG & Lozanov BS. Recombinant human TSH in radioiodine treatment of differentiated thyroid cancer. *Nucl Med Rev Cent East Eur* 2004; 7: 13-9.
22. Pacini F, Ladenson P, Schlumberger M, et al. Preparation with thyrotropin alfa is equivalent to thyroid hormone withdrawal as preparation for thyroid remnant ablation in differentiated thyroid carcinoma. Turk J Endocrinol Metab 2004; 8: 21.
23. Luster M, Sherman SI, Skarulis MC, et al. Comparison of radioiodine biokinetics following the administration of recombinant human thyroid stimulating hormone and after thyroid hormone withdrawal in thyroid carcinoma. *Eur J Nucl Med Mol Imaging* 2003; 30: 1371-7.
24. Adler ML, Macapinlac HA, Robbins RJ. Radioiodine treatment of thyroid cancer with the aid of recombinant human thyrotropin. *Endocr Pract* 1998; 4: 282-6.
25. Rudavsky AZ, Freeman LM. Treatment of scannegative, thyroglobulin-positive metastatic thyroid cancer using radioiodine 131I and recombinant human thyroidstimulating hormone [clinical case seminar]. *J Clin Endocrinol Metab* 1998; 82: 11-4.
26. Colleran KM, Burge MR. Isolated thyrotropin deficiency secondary to primary empty sella in a patient with differentiated thyroid carcinoma: an indication for recombinant thyrotropin. *Thyroid* 1999; 9: 1249-52.
27. Masiukiewicz US, Nakchbandi IA, Stewart AF, Inzucchi SE. Papillary thyroid carcinoma metastatic to the pituitary gland. *Thyroid* 1999; 9: 1023-7.
28. Vargas GE, Uy H, Bazan C, Guise TA, Bruder JM. Hemiplegia after thyrotropin alfa in a hypothyroid patient with thyroid carcinoma metastatic to the brain. *J Clin Endocrinol Metab* 1999; 84: 3867-71.
29. Perros P. Recombinant human thyroid-stimulating hormone (rhTSH) in the radioablation of well-differentiated thyroid cancer: preliminary therapeutic experience. *J Endocrinol Invest* 1999; 22: 30-4.
30. Luster M, Lassmann M, Haenscheid M, Michalowski U, Incerti C, Reiners C. Use of recombinant human thyrotropin before radioiodine therapy in patients with advanced differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2000; 85: 3640-5.
31. Mariani G, Ferdeghini M, Augeri C, et al. Clinical experience with recombinant human thyrotropin (rhTSH) in the management of patients with differentiated thyroid cancer. *Cancer Biother Radiopharm* 2000; 15: 211-7.
32. Robbins RJ, Voelker E, Wang W, Macapinlac HA, Larson SM Compassionate use of recombinant human thyrotropin to facilitate radioiodine therapy: case report and review of the literature. *Endocr Pract* 2000; 6: 460-4.
33. Lippi F, Capezzone M, Angelini F, et al. Radioiodine treatment of differentiated thyroid cancer on L-thyroxine plus recombinant human TSH (rhTSH): initial single-center experience. *Eur J Endocrinol* 2001; 144: 5-11.
34. Pellegritti G, Scollo C, Giuffrida D, Vigneri R, Squatrito S, Pezzino V. Usefulness of recombinant human thyrotropin in the radiometabolic treatment of selected patients with thyroid cancer. *Thyroid* 2001; 11: 1025-30.
35. Jarzab B, Handkiewicz-Junak D, Roskosz J, et al. Recombinant human TSH-aided radioiodine treatment of advanced differentiated thyroid cancer: single-center study of 54 patients. *Eur J Nucl Med Mol Imaging* 2003; 30: 1077-86.
36. Rotman-Pikielny P, Reynolds JC, Barker WC, Yen PM, Skarulis MC, Sarlis NJ Recombinant human thyrotropin for the diagnosis and treatment of a highly functional metastatic struma ovarii. *J Clin Endocrinol Metab* 2000; 85: 237-44.

37. Aslam SN, Daly RG. Use of recombinant human thyrotropin in a complicated case of metastatic papillary thyroid carcinoma. *Endocr Pract* 2001; 7: 99-101.
38. Checrallah A, Medlej R, Saade C, Khayat G, Halaby G. Malignant struma ovarii: an unusual presentation [case history]. *Thyroid* 2001; 11: 889-92.
39. Berg G, Lindstedt G, Suurküla M, Jansson S. Radioiodine ablation and therapy in differentiated thyroid cancer under stimulation with recombinant human thyroid-stimulating hormone (rhTSH). *J Endocrinol Invest* 2002; 25: 44-52.
40. Müller V, Bohuslavizki KH, Klutmann S, Clausen M. Value of recombinant human thyrotropin in high-dose radioiodine therapy: a case report. *J Nucl Med Technol* 2002; 30: 185-8.
41. Goffman T, Ioffe V, Tuttle M, Bowers JT, Mason ME. Near-lethal respiratory failure after recombinant human thyroid-stimulating hormone use in a patient with metastatic thyroid carcinoma [case history]. *Thyroid* 2003; 13: 827-30.
42. de Keizer B, Brans B, Hoekstra A, et al. Tumour dosimetry and response in patients with metastatic differentiated thyroid cancer using recombinant human thyrotropin before radioiodine therapy. *Eur J Nucl Med Mol Imaging* 2003; 30: 367-73.
43. Menzel C, Kranert WT, Döbert N, et al. rhTSH stimulation before radioiodine therapy in thyroid cancer reduces the effective half-life of 131I. *J Nucl Med* 2003; 44: 1065-8.
44. Driedger AA, Kotowycz N. Two cases of thyroid carcinoma that were not stimulated by recombinant human thyrotropin [clinical case seminar]. *J Clin Endocrinol Metab* 2004; 89: 585-90.
45. Taïeb D, Jacob T, Zotian E, Mundler O. Lack of efficacy of recombinant human thyrotropin versus thyroid hormone withdrawal for radioiodine therapy imaging in a patient with differentiated thyroid carcinoma lung metastases [case history]. *Thyroid* 2004; 14: 465-7.
46. Ashcraft MW, Van Herle AJ. The comparative value of serum thyroglobulin measurements and iodine 131 total body scans in the follow-up study of patients with treated differentiated thyroid cancer. *Am J Med* 1981; 71: 806-14.
47. Ronga G, Filesi M, Ventroni G, Vestri AR, Signore A. Value of the first serum thyroglobulin level after total thyroidectomy for the diagnosis of metastases from differentiated thyroid carcinoma. *Eur J Nucl Med* 1999; 26: 1448-52.
48. Franceschi M, Kusic Z, Franceschi D, Lukinac L, Roncevic S. Thyroglobulin determination, neck ultrasonography and iodine-131 whole-body scintigraphy in differentiated thyroid carcinoma. *J Nucl Med* 1996; 37: 446-51.
49. Montella L, Caraglia M, Abbruzzese A, et al. Molecular technology and the recombinant TSH have changed diagnostics of thyroid carcinoma with positive I-131 whole body scan but low serum thyroglobulin. *Exp Mol Med* 2004; 36: 268-73.
50. Muller-Gartner HW, Schneider C. Clinical evaluation of tumor characteristics predisposing serum thyroglobulin to be undetectable in patients with differentiated thyroid cancer. *Cancer* 1988; 61: 976-81.
51. Ronga G, Fiorentino A, Paserio E, et al. Can iodine-131 whole-body scan be replaced by thyroglobulin measurement in the post-surgical follow-up of differentiated thyroid carcinoma? *J Nucl Med* 1990; 31: 1766-71.
52. Schneider AB, Ikekubo K, Kuma K. Iodine content of serum thyroglobulin in normal individuals and patients with thyroid tumors. *J Clin Endocrinol Metab* 1983; 57: 1251-56.
53. Kohno Y, Tarutani O, Sakata S, Nakajima H. Monoclonal antibodies to thyroglobulin elucidate differences in protein structure of thyroglobulin in healthy individuals and those with papillary adenocarcinoma. *J Clin Endocrinol Metab* 1985; 61: 343-50.

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Es posible que la sabiduría y la ecuanimidad del hombre no constituyan hechos extraordinarios; tal vez tampoco lo sea que se afane por criar a sus hijos, que cuide con ahínco de sus padres, que obtenga su propio sustento, que se ponga a cubierto de los peligros y que sea dueño de las dotes brindadas por la Naturaleza, porque el ser humano tiene el don máximo del lenguaje, además de contar con los favores del razonamiento, un recurso de gran utilidad. Por otra parte, también brinda respeto y veneración a las divinidades.

Claudio Eliano (c 170-c 235)

Historia de los animales (*De Natura Animalium*). Prólogo. Madrid: Hyspamérica, 1985.
Traducción castellana de María Otero, p 11