Radioiodine Ablation of Postsurgical Thyroid Remnants After Treatment With Recombinant Human TSH (rhTSH) in Patients With Moderate-to-Severe Graves' Orbitopathy (GO): A Prospective, Randomized, Single-Blind Clinical Trial

Mariacarla Moleti, Maria Antonia Violi, Daniela Montanini, Costantino Trombetta, Beatrice Di Bella, Giacomo Sturniolo, Silvia Presti, Angela Alibrandi, Alfredo Campennì, Sergio Baldari, Francesco Trimarchi, and Francesco Vermiglio

Dipartimento di Medicina Clinica e Sperimentale, Sezione di Endocrinologia (M.M., M.A.V., B.D.B., G.S., S.P., F.T., F.V.); Dipartimento di Scienze Sperimentali Medico-Chirurgiche, Specialistiche ed Odontostomatologiche, Sezione di Oftalmologia (D.M., C.T.); Dipartimento di Scienze Economiche, Finanziarie, Sociali, Ambientali, Statistiche e del Territorio (A.A.); and Dipartimento di Scienze Radiologiche, Sezione di Medicina Nucleare (A.C., S.B.), University of Messina, 98122 Messina, Italy

Context: Recent evidence suggests thyroidectomy (Tx) followed by radioiodine remnant ablation to be beneficial to Graves' orbitopathy (GO) patients.

Objective: The aim of the study was to evaluate the effect of ^{131}I thyroid ablation after recombinant human TSH stimulation in patients with moderate-to-severe GO.

Design, Patients, and Interventions: The study was prospective, randomized, and single-blind, and it included 40 consecutive patients with moderate-to-severe GO randomized into: 1) a Tx-radioactive iodine (RAI) group (20 subjects who underwent total-Tx and ^{131}I ablation after recombinant human TSH stimulation); and 2) a Tx group (20 subjects who underwent total-Tx alone).

Outcome Measures: The overall GO outcome 12 months after Tx/radioiodine ablation was the main measure.

Results: GO evaluation at the end of iv glucocorticoids showed eye disease to be improved in 65% of the Tx-RAI group and 60% of the Tx group patients. At 6 and 12 months, no further changes in the GO outcome could be observed in the Tx-RAI group. Conversely, five patients from the Tx group exhibited a deterioration in GO. At 12 months, GO was found to be improved in 70% of the Tx-RAI and 20% of the Tx group patients, the latter being found to be stable (55%) or worse (25%) than at baseline evaluation. At 12 months, GO was found to be inactive in a significantly higher percentage of patients in the Tx-RAI than in the Tx group (75 vs 30%; $P < .01$).

Conclusions: Postoperative radioiodine ablation proved more effective than Tx alone in inducing earlier and steadier GO improvement in patients with moderate-to-severe GO treated with iv glucocorticoids over a 24-month follow-up period. **(*J Clin Endocrinol Metab* 99: 1783–1789, 2014)**

There is still no unanimous consensus on the best way to treat hyperthyroidism in patients with concomitant orbitopathy. In particular, the questions of whether treatment should be influenced by the severity and activity of eye disease and of whether it should be conservative or definitive remain contentious (1, 2). Some experts in this

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Abbreviations: BCVA, best corrected visual acuity; BW, body weight; CAS, clinical activity score; FT3, free T_3; FT4, free T_4; GC, glucocorticoids; GD, Graves' disease; GO, Graves' orbitopathy; IQR, interquartile range; L-T4, levothyroxine; NS, not significant; RAI, radioactive iodine; rhTSH, recombinant human TSH; Tg, thyroglobulin; TgAb, Tg antibody; TRAb, anti-TSH receptor antibody; Tx, thyroidectomy; US, ultrasound.

field believe that patients with moderate-to-severe Graves' orbitopathy (GO) should be treated with long-term antithyroid drug treatment until all treatments for GO are concluded and the eye disease does not require any further therapy (3). A more radical therapeutic approach involving both thyroidectomy (Tx) and radioactive iodine (RAI) ablation of postsurgical residual thyroid tissue (total thyroid ablation) has also been questioned (2). The rationale underlying this treatment is based on the theoretical postulate that total thyroid ablation, by removing both thyroid-orbit cross-reacting autoantigens and autoreactive T lymphocytes, would be beneficial in improving outcomes of orbitopathy. Our research group tested this hypothesis in a retrospective study of a series of patients with Graves' disease (GD) and associated mild GO who had undergone either Tx alone or total thyroid ablation. This study showed an earlier and more persistent improvement in GO in a significantly higher percentage of patients in the group that underwent Tx and radioiodine ablation than in the group that underwent Tx alone (4). A more recent randomized controlled clinical trial demonstrated that, as compared to total Tx alone, total thyroid ablation was followed by a better GO outcome in patients with mild-to-moderate and active eye disease given iv glucocorticoids (GCs) (5). Overall, these findings suggest that total thyroid ablation may prove clinically beneficial in patients with more severe or progressive and invalidating GO. However, prolonged hypothyroidism after withdrawal of levothyroxine (L-T4), which is necessary before the ablative dose of ^{131}I being given, is potentially hazardous because of the risk of GO worsening due to the hypothyroid state (6). In these cases, total thyroid ablation could be performed after recombinant human TSH (rhTSH) stimulation of ^{131}I uptake, allowing patients to remain euthyroid while on L-T4. Although Daumerie et al (7) recently reported three cases of GO reactivation in patients treated with rhTSH and radioiodine ablation, no systematic data are presently available regarding the employment of rhTSH in GO patients.

This study aims to verify the effects of rhTSH-aided radioiodine ablation on the course of moderate-to-severe GO and to establish whether rhTSH administration could have clinically significant ocular effects in these patients.

Patients and Methods

For the purposes of this investigation, consecutive patients affected with GD and associated moderate-to-severe GO referred to our Unit between 2006 and 2011 were invited to participate in the study and were assigned by a computer-generated random list to one of two treatment arms: 1) study group—total Tx and radioiodine ablation of postsurgical thyroid remnants after rhTSH stimulation (Tx-RAI group; n = 20 patients); and 2) control group—total Tx alone (Tx group; n = 20 patients).

No patient declined the invitation to participate in the study.

The number of patients to be included in the study was calculated by taking into account that, according to previous and unpublished data from our research group, the estimated GO improvement after Tx is approximately 25%. Assuming an expected difference between the two groups in the proportion of GO improvement after iv GCs (Δ) ranging from 40 to 50% (8), $\alpha = 0.05$, and a statistical power (1-β) of 0.8, the number of patients to be included for each group ranged between 15 and 24. Further considering a 10% dropout rate for reasons unrelated to GO, the sample size finally amounted to 20 subjects for each treatment arm.

Inclusion criteria were: 1) GD and GO onset ≤12 months; 2) no previous GD treatment other than antithyroid drugs; 3) no previous GO treatment other than local measures; 4) thyroid surgery indications (thyroid volume >15 mL and/or (multi)nodular goiter and/or poor hyperthyroidism control despite antithyroid drugs and/or poor compliance with treatment); 5) moderate-to-severe GO; 6) clinically active GO (clinical activity score [CAS] ≥3/7); and 7) informed consent.

Exclusion criteria were: 1) GD or GO onset >12 months; 2) previous GD radioiodine or surgical treatment; 3) previous GO treatment other than local measures; 4) mild GO; 5) urgent orbital surgical decompression; 6) cytological findings suspicious for thyroid malignancy and/or postsurgical histopathological evidence of thyroid malignancy; 7) pregnancy or breast-feeding; 8) contraindications to GCs; and 9) no informed consent.

Procedures

Before Tx, all patients were given antithyroid drugs (methimazole in all cases) until euthyroidism was restored. Total Tx was performed by excision of the whole gland, leaving no more than 1 g of thyroid tissue per lobe. Substitutive L-T4 was started within 1 week of Tx at the lowest dose required to maintain serum TSH values between 0.5 and 1.0 mU/L.

Residual thyroid tissue ablation was performed in all Tx-RAI group patients within 3–4 weeks of Tx by administration of a standard dose of 1110 MBq (30 mCi) of ^{131}I after rhTSH preparation. In detail, on days 1 and 2, rhTSH was given im as a single 0.9-mg dose; on day 3, residual thyroid tissue size was evaluated by anterior cervical ultrasound (US), and the standard ablative dose of ^{131}I was administered; on day 4 (24 h after administration of ^{131}I), cervical uptake was calculated.

Serum thyroglobulin (Tg) and TSH concentrations were measured in all patients before radioiodine ablation.

The effectiveness of ablation was evaluated 9–12 months after radioiodine treatment following rhTSH stimulation. Ablation was considered successful when serum Tg values remained <1 ng/mL over the 5 days after rhTSH stimulation (rhTSH-Tg testing).

Intravenous GCs (methylprednisolone acetate) were given to all patients in both groups 45 days after surgery (Tx group) or radioiodine ablation (Tx-RAI group) according to the following protocol: two iv infusions of methylprednisolone acetate on alternate days each week for 6 weeks, at a dosage of 15 mg/kg body weight (BW) for the first two infusions (first week of treatment), 7.5 mg/kg BW for the following four infusions (second and third weeks of treatment), and 3.75 mg/kg BW for the last six infusions (fourth, fifth, and sixth weeks of treatment). Accordingly, the cumulative dose of iv GCs ranged between 4.5 and 7.5 g.

Overall, 22 patients (six from the Tx-RAI group and 16 from the Tx group), whose GO was found to be either stable or deteriorated at 6 or 12 months with respect to the baseline assessment, received a second course of iv GCs.

Neither surgical complications nor major adverse events after iv GCs occurred in any patients.

Apart from a mild BW gain, which was recorded in almost 40% of patients (15 of 40), a transient hyperglycemia was observed in three patients (one Tx-RAI group patient and two Tx group patients).

Serum assays

Serum TSH, free T_3 (FT3), free T_4 (FT4), antibodies to Tg (TgAb) and to thyroperoxidase (electrochemiluminescence immunoassay) were determined using commercial kits supplied by Roche Diagnostics. Anti-TSH receptor antibodies (TRAbs) were measured by radioimmune assay (Brahms Trak Human RIA, supplied by Dasit SpA). Serum Tg was immunoradiometrically measured (Thyroglobuline IRMA; Cisbio Bioassays). Normal values were: TSH, 0.27–4.2 mIU/L; FT3, 2.0–4.4 pg/mL; FT4, 12.0–22.0 pmol/L; TRAb, <1 IU/L; TgAb, 0–115 IU/mL; thyroperoxidase antibody, 0–34 IU/mL; Tg, 0–40 ng/mL.

GO evaluation

Ophthalmological examination was performed in all patients by the same two physicians (FV and DM), who were blinded to the treatment used, throughout the entire observation period.

GO was evaluated and graded in accordance with EUGOGO recommendations for clinical assessment of patients with GO (9, 10) and included: 1) measurement of lid width; 2) evaluation of soft-tissue involvement, using a comparative photographic color atlas (www.eugogo.eu); 3) measurements of proptosis by Hertel exophthalmometer; 4) assessment of extraocular muscle function and diplopia; 5) evaluation of corneal involvement; 6) evaluation of optic nerve involvement; and 7) eye disease activity evaluation, using the CAS (11).

GO improvement was defined as changes in two or more of the following outcome measures in at least one eye, without deterioration in the opposite eye: 1) reduction of CAS $\geq$2 points; 2) reduction of eyelid width $\geq$2 mm; 3) reduction in proptosis $\geq$2 mm; 4) improvement in diplopia (disappearance/change in degree); and 5) improvement in best corrected visual acuity (BCVA) by $\geq$ two lines on Snellen chart.

Conversely, GO worsening was defined as changes in two or more of the following outcome measures in at least one eye: 1) increase of CAS $\geq$2 points; 2) increase of eyelid width $\geq$2 mm; 3) increase in proptosis $\geq$2 mm; 4) worsening in diplopia (appearance/change in degree); and 5) reduction in BCVA by $\geq$ two lines on Snellen chart. GO was considered stable in the absence of changes or when changes were smaller than any of the above-defined parameters.

Primary and secondary end points and timing of observation

The primary end point was overall GO outcome 12 months after Tx/radioiodine ablation. GO outcome at 18 and 24 months was also assessed with the aim of evaluating either the maintenance of the response recorded at 12 months or the response of patients having undergone a second course of iv GCs.

Secondary end points included: 1)short-term GO outcomes (at 45 d, and at 3 and 6 mo); and 2) the effects of acute rhTSH and ^{131}I administration on GO.

All patients underwent GO evaluation according to the following schedule: 1) Tx group—just before Tx, 45 days after Tx (ie, immediately before iv GCs), 3 months after Tx (ie, at the end of iv GCs), and 6, 12, 18, and 24 months after Tx; and 2) Tx-RAI group—just before Tx, just before thyroid remnant ablation (on d 3), 45 days after thyroid remnant ablation (ie, immediately before iv GCs), 3 months after thyroid remnant ablation (ie, at the end of iv GCs), 6, 12, 18, and 24 months after thyroid remnant ablation and on day 3 after rhTSH administration for Tg testing.

Informed consent was obtained using a form approved by the local ethical committee after full discussion of the protocol's inclusion-exclusion criteria, methodologies, and patient protection procedures.

Statistical analysis

Numerical data are expressed as median, interquartile range (IQR), and mean $\pm$ SD, and categorical variables are expressed as numbers and percentages. Statistical analyses were performed using SPSS 11.0 for Windows (SPSS Inc) and Methodologica srl, 2001, NPC Test 2.0 (Methodologica srl). All examined variables (lid width, proptosis, CAS, visual acuity) were normally distributed, as verified by Kolmogorov-Smirnov test. Nonetheless, because distribution of the above parameters in the general population is not normal, the nonparametric approach has been used (Mann-Whitney test to compare the two groups; Wilcoxon test to compare each parameter at two different and consecutive points in time within each group). χ^2 or Fisher exact test (when appropriate) and log-likelihood ratio test were performed to compare categorical data at baseline and at the end of the study period. $P < .05$ was considered to be statistically significant.

Results

Baseline characteristics of the patients are shown in Table 1 and indicate that, at presentation, no significant difference was present between the two groups.

The presence and volume of postsurgical thyroid remnants were assessed by US within 1 month of Tx in the Tx group and immediately before the ^{131}I ablative dose was administered in the Tx-RAI patients. Thyroid remnants were detected by US in 14 of 20 (70%) Tx group patients and in 13 of 20 (65%) Tx-RAI group patients (mean volume, 0.53 $\pm$ 0.48 and 0.59 $\pm$ 0.44 mL, respectively; P = not significant [NS]). In the latter group, cervical uptake was also measured 24 hours after administration of ^{131}I. Mean thyroid bed uptake was 5.19 $\pm$ 4.54% (median, 3.7%; range, 0.3–15%). To assess the effectiveness of ablation, 16 of 20 Tx-RAI patients who tested negative for TgAb underwent rhTSH-stimulated Tg determination. Serum Tg levels proved below 1 ng/mL in 15 of 16 (93.7%) patients and above this limit (2.4 ng/mL) in one patient.

Table 1. Epidemiological, Biochemical, and Clinical Features of the Two Groups Before Tx

	Tx-RAI Group	Tx Group	*P*
N	20	20	
No. of women/men	11/9	14/6	NS
Age, median (range), y	46 (19–61)	47 (19–65)	NS
Smokers, n (%)	7 (35)	6 (30)	NS
GD duration, mo	6.2 ± 3.1	6.4 ± 2.2	NS
GO duration, mo	5.7 ± 2.7	5.6 ± 2.6	NS
Biochemical parameters			NS
FT3, pg/mL	3.14 ± 0.48	3.08 ± 0.43	
FT4, pmol/L	14.9 ± 0.9	14.3 ± 1.0	
TSH, mU/L	1.25 ± 0.58	1.41 ± 0.61	
TRAb, IU/L	8.1 ± 6.9	7.2 ± 5.4	
Lid width, mm[a]			NS
Median	14.5	14.5	
IQR	11.75–16.25	11.75–15.25	
Mean ± SD	14.1 ± 3.0	14.2 ± 2.9	
Proptosis, mm[a]			NS
Median	25	24.5	
IQR	22–27	22.75–26.25	
Mean ± SD	24.8 ± 3.4	24.9 ± 2.4	
CAS			NS
Median	6.0	5.0	
IQR	5.0–6.0	4.75–5.25	
Mean ± SD	5.6 ± 1.0	5.1 ± 0.9	
Diplopia (Bahn and Gorman's score)			
Inconstant, n (%)	13 (65)	14 (70)	NS
Constant, n (%)	7 (35)	6 (30)	NS
Visual acuity (decimal notation)[a]	0.58 ± 0.22	0.68 ± 0.21	NS

Data are expressed as mean ± SD, unless otherwise specified.

[a] Most affected eye.

All patients were euthyroid at each clinical evaluation, and no differences between the two groups were found in FT3, FT4, or TSH levels. Nor were the cumulative iv GC doses different between the two groups (mean methylprednisolone dose—Tx-RAI group, 5.8 ± 0.83 g; Tx group, 6.0 ± 0.89 g).

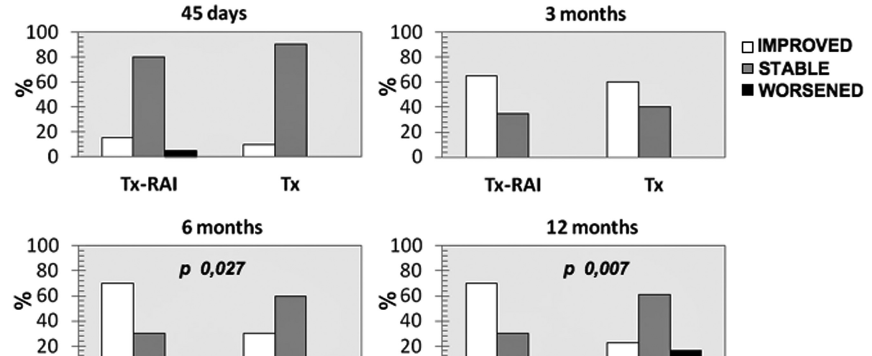

Figure 1. GO clinical outcome at each point in time over the whole follow-up period in the two groups.

TRAbs were detected in all patients of both groups. TRAb titer decreased in both groups over the study period by the same extent, with no differences in the rate of patients with disappearance of TRAb from serum at the end of the follow-up period (65% of the Tx-RAI group and 60% of the TX group).

GO outcome in the short term and at 12 months

GO clinical outcomes at each stage in the follow-up period are shown in Figure 1. Clinical evaluation at 45 days after Tx or radioiodine ablation (before iv GCs) revealed no significant changes in GO features in either group, with the exception of three of 20 (15%) Tx-RAI and two of 20 (10%) Tx patients in whom a clinically detectable improvement was observed (*P* = NS). In addition, one Tx-RAI patient experienced a transient worsening of his eye disease. Evaluation at 3 months, ie, at the end of iv GCs, showed eye disease to be improved in 12 of 20 (60%) patients of both groups and unchanged in the remaining patients, with no significant difference between the two study groups. At subsequent follow-up (6 and 12 months), GO was found to be improved in two further patients in the Tx-RAI group. Conversely, five patients from the Tx group, two at 6 months and three more at 12 months, exhibited a deterioration in GO, consisting of reappearance/worsening of diplopia and increase in CAS in four of them, and increase in CAS and reduction in BCVA in the last one.

Overall, GO outcome was significantly better in the Tx-RAI group than in the Tx group at both 6 and 12 months ($P < .05$ and $P < .01$, respectively).

Changes in individual GO parameters in the two groups (baseline vs 12-month evaluation) are shown in Table 2.

A significant reduction in CAS was observed in the Tx-RAI group from the evaluation at 45 days after radioiodine ablation onward. In the Tx group, CAS significantly decreased between 45 days and 3 months and plateaued thereafter (Figure 2). At 12 months, mean CAS was significantly lower in the Tx-RAI group than in the Tx group (1.85 ± 1.56 vs 3.35 ± 2.03; $P < .05$).

The distribution of active and inactive eye disease in the two groups over the study period is reported in Figure 3. At 12 months, eye disease was found to be inactive in a significantly higher percentage of patients in the Tx-RAI than in the Tx group (15 of 20 Tx-RAI vs 6 of 20 Tx; *P* = .01).

Table 2. Overall Changes in Individual GO Parameters in the Two Groups

GO Parameters	Tx-RAI Group			Tx Group			
	Baseline	**12 mo**	***P*[b]**	**Baseline**	**12 mo**	***P*[b]**	***P***
Proptosis, mm[a]							
Median	25	22		25	26		
IQR	22–27	20–25	<.0001	22–27	24–27	NS	<.05
Mean ± SD	24.8 ± 3.4	22.1 ± 3.8		24.9 ± 3.4	25.1 ± 2.6		
Lid width, mm[a]							
Median	14.5	12		14.5	12		
IQR	11.75–16.25	10–14	<.0001	11.75–15.25	11–14	<.005	NS
Mean ± SD	14.1 ± 3.0	12.4 ± 2.5		14.2 ± 2.9	12.5 ± 2.3		
CAS							
Median	6.0	1.5		5.0	3		
IQR	5.0–6.0	1–2.5	<.00001	4.7–5.2	2–5	<.05	.005
Mean ± SD	5.6 ± 1.0	1.8 ± 1.6		5.1 ± 0.9	3.3 ± 2.1		
Diplopia, n (%)							
Absent		7 (35)			2 (11.1)		
Intermittent		10 (50)	<.0001		4 (22.2)	NS	<.05
Inconstant	13 (65)	2 (10)		14 (70)	9 (50)		
Constant	7 (35)	1 (5)		6 (30)	3 (16.6)		
Visual acuity[a]							
Decimal notation, mean ± SD	0.58 ± 0.22	0.82 ± 0.12	<.0005	0.68 ± 0.21	0.8 ± 0.17	<.0005	NS

The last column refers to statistical analysis of the two groups at the end of the study period.

[a] Most affected eye.

[b] Differences within the groups.

GO outcome at 18 and 24 months

All patients from both groups classified as improved at 12 months did not show any significant changes in their GO at either 18 or 24 months. Although a further reduction in mean CAS values was observed in these patients, this was not statistically significant.

GO outcome in patients who had undergone a second course of iv GCs

Overall, six of 20 Tx-RAI and 16 of 20 Tx patients required a second course of iv GCs because of the persistence (six Tx-RAI and 11 Tx patients) or worsening (five Tx patients) of clinical GO signs. In detail, two Tx patients exhibited a remarkable GO deterioration at 6 months, which required the prompt administration of a second course of iv GCs. All the remaining patients (six of the Tx-RAI and 14 of the Tx group) were given a second course of iv methylprednisolone after the evaluation at 12 months.

Figure 4 shows GO outcome in patients who had undergone the second course of iv GCs. Overall, the rate of GO improvement was the same in the two groups at each point in time (3 months, 83.3 and 87.5% in the Tx-RAI and Tx groups, respectively; 6 and 12 months, 66.6 and 68.7% in the Tx-RAI and Tx groups, respectively). Although a definite progression of GO was not observed in any patients in the two groups, two patients in the Tx-RAI group and five in the Tx group failed to show any improvement also after the second course of iv GCs, the difference between the two groups being not statistically significant.

Acute effect of rhTSH and of ^{131}I administration on GO

To assess the ocular safety of acute rhTSH administration, all patients from the Tx-RAI group underwent GO

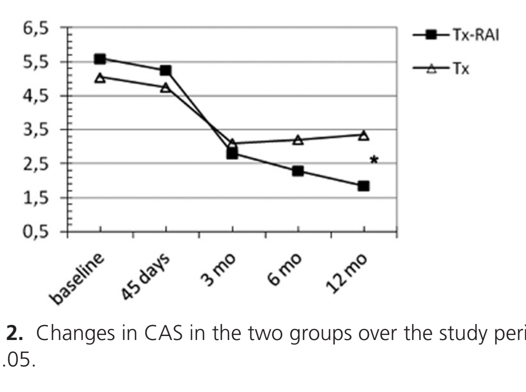

Figure 2. Changes in CAS in the two groups over the study period. *, $P < .05$.

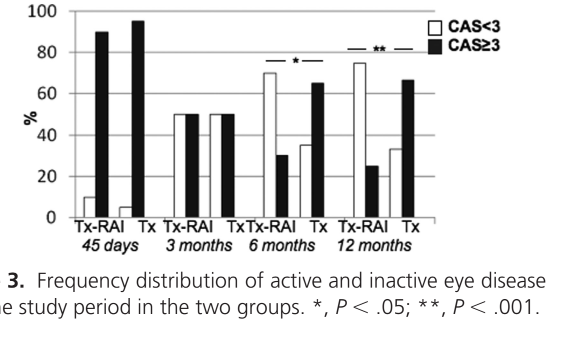

Figure 3. Frequency distribution of active and inactive eye disease over the study period in the two groups. *, $P < .05$; **, $P < .001$.

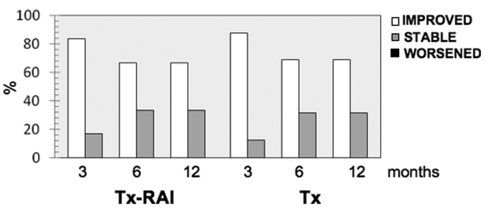

Figure 4. GO clinical outcome at 3, 6, and 12 months after the second course of iv GCs (Tx-RAI group, n = 6 patients; Tx group, n = 16 patients).

evaluations 3 days after rhTSH administration for radioiodine ablative treatment. An additional GO evaluation was also performed on day 3 in 16 of 20 TgAb-negative patients of the Tx-RAI group who underwent rhTSH-Tg testing for ablation assessment. No patient complained of clinically significant ocular effects after rhTSH administration, except for a transient aggravation in retrobulbar pain in one patient after the first rhTSH administration.

Discussion

The belief that both the thyroid and ocular diseases are caused by the same autoimmune disorder (12), along with the knowledge that long-term maintenance of euthyroidism is essential for a good outcome of the eye disease (6, 13), provided the theoretical basis for considering total thyroid ablative therapy in patients with clinically significant ocular disease (14–16). This topic has recently been the focus of four different studies. The first was carried out by our research group in 2003 on a retrospective series of patients with mild GO who underwent radioiodine ablation of postsurgical thyroid remnants because of histological evidence of differentiated thyroid carcinoma. The main finding of this study was that the ocular disease became and/or remained inactive in a significantly higher proportion of subjects who underwent total ablation than in those who underwent Tx alone (4). Similarly, in 2007, Menconi et al (5) carried out a randomized, controlled clinical trial demonstrating that, compared with total Tx alone, total thyroid ablation yielded better GO outcomes in patients given iv GCs over a follow-up period of 9 months. More recently, the same research group evaluated GO outcomes in a subset of patients from the previous study over a longer observation period. At the end of the follow-up, GO outcome was found to be similar in both groups, although the total thyroid ablation group achieved a greater improvement over a shorter period than patients from the Tx alone group (17). Finally, De Bellis et al (18) found no difference in GO outcome at 24 months between 25 patients who underwent Tx alone and 10 patients in whom Tx was followed by radioiodine ablation of residual thyroid tissue.

Taken together, the data currently available suggest that total thyroid ablation induces an earlier improvement and a more favorable GO outcome than Tx alone. However, in the long term (approximately 24–36 mo after surgery), both therapeutic procedures prove to be effective to a similar extent. The latter observation indicates that total thyroid ablation may somehow interfere with the natural history of the eye disease, perhaps by inducing a faster attenuation of autoimmunity toward the orbital tissues. The results of our study seem to support this hypothesis. Indeed, the overall outcome of GO in the two groups, not different at 3 months (ie, at the end of treatment with iv GCs), was significantly better at both 6 and 12 months in patients who underwent total thyroid ablation than in those treated by Tx alone. It is worth noting that the difference observed was due not to a further increase in the proportion of patients in the Tx-RAI group who improved, but rather to a reduction in the number of patients in the Tx group that could be classified as improved. In other words, a significant percentage of Tx patients did not maintain the improvement initially achieved and were later found to be stable or worse than at baseline evaluation. This finding was reflected by markedly different CAS scores in the two groups: in the Tx-RAI group, mean CAS decreased steadily and significantly over the follow-up period, and the eye disease became inactive in an increasing proportion of patients; in the Tx group, on the other hand, not only was the decrease in mean CAS values lower than that observed in the Tx-RAI group, but the eye disease was also found to be active at 6 and 12 months in a significantly higher proportion of patients.

The prolongation of the study period up to 24 months after surgery/radioiodine ablation revealed the GO improvement observed at 12 months to be confirmed in the long term in all patients from both groups. On the other hand, 22 patients (six from the Tx-RAI group and 16 from the Tx group) needed a second course of iv GCs because of the persistence/recurrence of clinical GO signs at 6–12 months. The response rates after the second course of iv GCs was similar (about 70%) in the two groups, eventually yielding a total of 18 Tx-RAI group and 15 Tx group patients improved at the end of the follow-up period (24 months), ie, in a similar number of subjects. Nonetheless, some considerations need to be made. First, a second course of iv GCs was required in a significantly higher proportion of patients who underwent Tx alone than in those who underwent total ablation, a circumstance that is not insignificant when the potential for adverse events associated with high-dose iv GCs is taken into account. Secondly, but equally important, an earlier and persistent inactivation of GO occurred among patients treated by total thyroid ablation. This finding has obvious clinical implications because GO inactivation is a requirement for any rehabilitative surgery to be made, if needed.

Another objective of this study was to evaluate the safety of rhTSH in patients with GO. To the best of our knowledge, this topic has never been systematically investigated. To date, one case of GO appearance after administration of 13-cis-retinoic acid and rhTSH has been reported in the literature (19) and, more recently, Daumerie et al (7) reported three cases of reactivation of GO in patients who underwent treatment with rhTSH and radioiodine ablation. In another report, however, rhTSH was successfully used in preparation for postoperative radioiodine remnant ablation in a woman with differentiated thyroid carcinoma and concomitant GO, with no changes in her eye disease (20).

In our patients, rhTSH was given twice: first before administering the ^{131}I ablative dose, and then 9–12 months after radioiodine ablation to verify its effectiveness. Our data demonstrate that rhTSH in GO patients is safe and unaccompanied by significant adverse ocular effects. Indeed, with the exception of one patient who experienced a transient exacerbation in retrobulbar pain, no side effects or worsening in GO clinical signs were observed.

In conclusion, this is the first study addressing the issue of thyroid remnant ablation using rhTSH in patients with GO. Our results indicate that postoperative radioiodine ablation is more effective than Tx alone in inducing earlier and steadier GO improvement in patients with moderate-to-severe GO treated with iv GCs, at least over a 24-month follow-up period. Further studies investigating the overall benefits and risks of this procedure are warranted before any conclusions can be drawn. Nonetheless, the finding that rhTSH in GO patients is safe, in our view, indicates rhTSH-aided total thyroid ablation to be an attractive option for patients with GO because it prevents the risk of any detrimental ocular effects resulting from L-T4 withdrawal hypothyroidism.

Acknowledgments

Address all correspondence and requests for reprints to: Francesco Vermiglio, Via Consolare Valeria, 1-98100 Messina, Italy. E-mail: fvermiglio@unime.it.

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