Endocrine (2012) 41:320–326
DOI 10.1007/s12020-011-9559-x

ORIGINAL ARTICLE

Time course of Graves' ophthalmopathy after total thyroidectomy alone or followed by radioiodine therapy: a 2-year longitudinal study

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Received: 14 September 2011 / Accepted: 22 November 2011 / Published online: 16 November 2011

Abstract The findings in hyperthyroid patients with Graves' orbitopathy (GO) of antibodies against antigens shared between the thyroid and orbit, such as the TSH-receptor (TRAb) and a novel protein G2s (G2sAb), suggested a possible common therapeutic strategy. However, the gold therapeutic standard for hyperthyrodism in these patients remains still unsettled and is mainly based on personal experience. Studies on the effect of total thyroidectomy (TT) alone or followed by radioiodine ablation (RAI) of thyroid remnants showed often conflicting results. This longitudinal study was aimed at evaluating the influence of TT alone or followed by post-surgical RAI with respect to methimazole treatment on the activity and severity of GO in patients with hyperthyroidism and GO. Sixty consecutive patients with Graves' disease and mild/moderate GO were studied and grouped as follows: group 1, including 25 patients (16F, 9M) undergoing TT alone; group 2, including 10 patients (8F, 2M) undergoing TT followed by RAI for histological evidence of differentiated thyroid cancer; group 3, including 25 patients (18F, 7M) euthyroid under methimazole therapy, studied as controls. Clinical study of ophthalmopathy and measurements of TRAb and G2sAb were performed in all patients at start of the study (time of TT for group 1 and RAI after TT for group 2 and of the first finding of euthyroidism under methimazole treatment for group 3) and after 6, 12, 24 months. Patients of both groups 1 and 2 showed an early significant decrease and a further progressive reduction of the activity and severity of GO with a disappearance of TRAb and a decrease of G2sAb levels during the follow-up, without statistically significant differences between the two groups. Patients in group 3 showed a much later and less marked improvement of GO with persistence of TRAb and G2sAb positivity, even if with reduction of TRAb levels at 12 and 24 months. Our results suggest that in Graves' patients with large goiter or relapse of hyperthyroidism and mild/moderate GO, TT alone could be an advisable choice to treat hyperthyroidism also improving GO with reduction of cost/benefit ratio.

Keywords Thyroidectomy · Ocular parameters · TRAb · G2sAb · Graves' ophthalmopathy

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Introduction

Graves' ophthalmopathy (GO) is an autoimmune disease characterized by inflammation of retro-orbital tissues (connective/adipose tissue and extraocular muscles), that remains a pathogenic and therapeutic dilemma up to now [1, 2].

The close association between ophthalmopathy and autoimmune thyroid diseases could depend on the presence

of thyroid and orbit shared antigens [3]. The strongest candidate at the present time is the TSH-receptor (TSH-R), expressed also in the orbital pre-adipocites/fibroblasts [4, 5]. Another putative shared antigen seems to be a novel protein called G2s, found both in the extraocular muscles and the thyroid, but not in orbital connective or adipose tissue [6]. Although the pathogenic role of G2s in GO remains to be still clarified, antibodies against G2s (G2sAb) have been proposed as good markers of ongoing autoimmune process involving extraocular muscles [7, 8].

Considering the relationship between autoimmune ocular and thyroid disease, the complete thyroid ablation could be an ideal treatment of ophthalmopathy in Graves' diseases (GDs) because it removes not only thyroid antigens shared with orbit, but also intrathyroid autoreactive T lymphocytes homing to orbit [9, 10]. Moreover, total thyroidectomy (TT) with respect to near-total/subtotal thyroidectomy is able to avoid the worsening of thyroid humoral autoimmunity and the relapse of hyperthyroidism [11, 12]. Nevertheless, results on the influence of TT on GO so far reported are controversial, probably due to the difficulty to obtain a complete ablation of thyroid tissue with surgical procedure [13, 14]. A better therapeutic strategy could be TT followed by radioiodine: in fact, even if radioiodine ablation (RAI) for GD is usually associated with small but increased risk of development or worsening of GO [15], the use of post-surgical RAI to ablate thyroid remnants could be useful to remove completely antigens shared with orbit [2]. However, this procedure is usually limited to GD with thyroid cancer.

To evaluate the influence of TT on the course of GO and the behavior of serum TRAb and G2sAb, we planned to study longitudinally possible clinical variations of some ocular parameters and serum levels of the above-mentioned antibodies in patients with GO submitted to TT alone or TT followed by RAI, comparing the results to those in patients treated with methimazole.

Patients and methods

We studied 60 consecutive patients (42F, 18M mean age 36.5 ± 4.8 SD) with GD and mild/moderate ophthalmopathy from 1998 to 2008. Criteria for enrollment were: active and mild/moderate GO and presence of TRAb and G2sAb. Patients with severe ophthalmopathy and/or optic nerve involvement were excluded because they needed other therapeutic approaches.

Indications for TT in groups 1 and 2 patients were: presence of large goiter or relapse of hyperthyroidism after stopping of anti-thyroid treatment. All patients were submitted to thyroid surgery 3 months after recovery of euthyroidism with methimazole treatment but without improvement of initial ocular conditions.

The preoperative thyroid volume was ≥60 ml in all patients (range 60–83 ml). Thyroidectomy was considered total when complete extracapsular removal of both two lobes and the isthmus was performed [14].

Graves' patients were grouped as follows: group 1, including 25 patients (16F, 9M) with mild/moderate ophtalmopaty who underwent TT alone; group 2, including 10 patients (8F, 2M), with mild/moderate ophthalmopathy who were submitted to a single standard dose of 131 I (1110 MBq) approximately 5 weeks after TT (when they became hypothyroid) to ablate thyroid remnant, because of histological findings indicating foci of differentiated thyroid carcinoma within the Graves' goiter (7/10 papillary, 3/10 follicular); group 3, including 25 Graves' patients (18F, 7M) with mild/moderate ophthalmopathy, euthyroid under methimazole treatment, studied as controls. The three groups of patients were matched for age, sex, duration of hyperthyroidism, smoking habits and ocular parameters at the enrollment.

All patients had normal thyroid hormone levels during all the follow-up: patients in group 1 had TSH levels between 0.5 and 1.0 μIU/ml under substitutive doses of thyroxine, while those in group 2 had TSH values ≤0.1 μIU/ml under suppressive doses of thyroxine. Patients in group 3 were euthyroid under methimazole treatment.

The ocular parameters, previously evaluated in line with the recommendations of the International Thyroid Association [16], were revised according to the European Group of Graves' orbitopathy (EUGOGO) for the definition of the severity of disease [17, 18]. The activity of disease was assessed using the Clinical Activity Score (CAS) [16, 18, 19].

In particular, all patients showed moderate soft tissue swelling, intermittent diplopia and proptosis ranging from 20 to 22 mm. Moreover, they had a CAS ≥4 and were positive for TRAb and G2sAb.

Ocular parameters and serum TRAb and G2sAb levels were evaluated at the start of the study in all patients and after 6, 12, and 24 months. The start of the study was the time of surgery for patients in group 1, the time of RAI after TT for those in group 2 and the time of first finding of euthyroidism under methimazole therapy for patients in group 3.

None of patients had received any specific treatment for ophthalmopathy before the inclusion in this study.

All patients gave their informed consent to participate to the study and the study protocol was approved by the local institutional Review Board.

Ocular evaluation

Ocular examination was performed by the same ophthalmologist throughout the study and included: evaluation of

soft tissue changes, measurement of proptosis (Hertel exopthalmometer), lid width and lagophtalmos, eye muscle function (Hess chart, red-green screen), and determination of visual acuity. Since the orbits were not always equally affected, we used the mean values.

TRAb determination

TRAb were measured by a second-generation TSH binding inhibitory assay based on the human recombinant TSH-receptor (B.R.A.H.M.S TRAK human RIA, B.R.A.H.M.S. AG, Hennigsdorf/Berlin, Germany) [20]. Values ≥1.5 IU/l were considered as positive.

G2sAb determination

A standard enzyme-linked immunosorbent assay (ELISA) was performed to measure antibodies to G2s as previously described [6]. A positive test was defined as an optical density (OD) more than the mean +2SD for a panel of 10 age and sex-matched normal subjects. The mean ± SD for normal controls was 0.109 ± 0.06 OD.

Statistical analysis

Data are expressed as mean ± SD, unless otherwise specified. Differences between frequencies were evaluated by Chi-square test. Non-parametric tests were used because of the non-Gaussian distribution of the data. Differences among the groups were evaluated with Kruskall–Wallis and Mann–Whitney U-test. The comparisons within each subgroup were evaluated using Wilcoxon test. A $P < 0.05$ was considered statistically significant.

Results

Baseline epidemiological characteristics, ocular parameters, and serum autoantibodies of the three groups of patients are summarized in Table 1. No significant differences of these parameters were observed between the three groups at the start of the study, except for thyroid volume significantly smaller in group 3 patients ($P < 0.05$) versus both groups 1 and 2 patients.

Longitudinal behavior of ocular parameters and of serum autoantibodies from the start of the study to the end of the follow-up span are summarized in Table 2.

Activity of GO

At 6 months, CAS decreased significantly with respect to the starting values in both groups 1 ($P = 0.001$) and 2 ($P < 0.04$) without any further variations during the follow-up. In group 3 CAS decreased significantly only at 12 and 24 months ($P = 0.002$ and 0.001, respectively) (Table 2).

Table 1 Baseline characteristics of Graves' patients with mild/moderate ophthalmopathy submitted to total thytoidectomy (TT) alone (group 1), to TT followed by I131 (group 2) and during methimazole therapy (group 3)

	Group 1 no. 25	Group 2 no. 10	Group 3 no. 25	*P*
Age (years)	36.10 ± 4.93	37.05 ± 5.0	37.02 ± 5	NS
Sex (M/F)	9/16	2/8	10/15	NS
Current smokers (No)	11	4	12	NS
Duration of hyperthyroidism (months)	21.23 ± 11.2	22.6 ± 9.2	22.2 ± 10.5	NS
Thyroid volume	73 ± 5.4	72 ± 4.9	31.9 ± 6.7*	<0.05
FT3 pg/ml	5.02 ± 0.7	5.3 ± 0.6	5.6 ± 0.5	NS
FT4 ng/ml	14.1 ± 1.5	14.7 ± 1.4	14.6 ± 1.2	NS
TSH μIU/ml	1.4 ± 0.3	1.5 ± 0.2	1.3 ± 0.5	NS
TRAb (n.v. ≤ 1.5 IU/l)	9.08 ± 2.5	8.9 ± 2.7	9.48 ± 3.38	NS
G2sAb (n.v. ≤ 0.12 OD)	0.43 ± 0.04	0.44 ± 0.08	0.42 ± 0.06	NS
Duration of ophthamopathy (months)	8.5 ± 1.3	8.7 ± 3.5	8.9 ± 2.9	NS
CAS	4.5 ± 0.5	4.2 ± 0.4	4.25 ± 0.44	NS
Lid width	10.69 ± 1.47	10.74 ± 1.52	10.59 ± 1.33	NS
Proptosis (mm)	21.54 ± 0.52	21.8 ± 21.45	21.83 ± 0.56	NS
Diplopia				
0	0	0	0	NS
1	25	10	25	
2	0	0	0	
3	0	0	0	

0 no diplopia, *1* intermittent, *2* inconstant, *3* constant, $P < 0.005$ versus groups 1 and 2

Table 2 Ocular parameters and behavior of TRAb and G2sAb before (A) and 6 (B), 12 (C), 24 (D) months after total thyroidectomy (TT) alone (group 1), TT followed by RAI (group 2) and during methimazole treatment (group 3) in Graves' patients with moderate ophthalmopathy

Disease activity	Group 1 no. 25				Group 2 no. 10				Group 3 no.25			
	A	B	C	D	A	B	C	D	A	B	C	D
CAS	4.5 ± 0.52	2 ± 0.69*	1.9 ± 0.64*	1.7 ± 0.75*	4.2 ± 0.45	1.6 ± 0.2$^{\#}$	1.4 ± 0.5$^{\#}$	1.1 ± 02$^{\#}$	4.2 ± 0.4	3.8 ± 0.9	2.9 ± 1.46$^{\infty}$	1.8 ± 0.8*
Disease severity												
Proptosis	21.5 ± 0.5	19.6 ± 0.9*	19.3 ± 0.9$^{\infty}$	19 ± 0.88*	21.8 ± 0.45	19.4 ± 0.55*	19 ± 0.73$^{\#}$	18.92 ± 0.4$^{\#}$	21.8 ± 0.56	21.79 ± 0.8	21.3 ± 1.4	20.7 ± 0.7
Diplopia												
0	0	24*	24*	24*	0	10$^{\infty}$	10$^{\infty}$	10$^{\infty}$	0	3	9	9$^{\bullet}$
1	25	1	1	1	10	0	0	0	25	21	11	11
2	0	0	0	0	0	0	0	0	0	1	3	0
3	0	0	0	0	0	0	0	0	0	0	0	0
Autoantibodies												
TRAb (n.v. $\leq$ 1.5 IU/l)	9.08 ± 2.5	1.5 ± 0.9*	1.3 ± 0.7*	1.2 ± 0.54*	8.9 ± 2.8	1.5 ± 0.5$^{\#}$	1.1 ± 0.3$^{\#}$	0.9 ± 1.1$^{\#}$	9.5 ± 3.4	7.4 ± 5.5	6.4 ± 6.3$^{\#}$	4.1 ± 2.7$^{\#}$
G2sAb (n.v. $\leq$ 0.12OD)	0.4 ± 0.04	0.26 ± 0.05*	0.24 ± 0.05*	0.23 ± 0.05	0.4 ± 0.09	0.3 ± 0.04$^{\#}$	0.2 ± 0.04$^{\#}$	0.2 ± 0.04$^{\#}$	0.4 ± 0.06	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.7

Data are expressed as mean ± SD; five patients in group 3, showing a worsening during the follow-up, were excluded from the study because required specific treatment for GO

* $P = 0.001$; $^{\infty}$ $P = 0.002$; $^{\bullet}$ $P = 0.003$; $^{\#}$ $P < 0.04$ versus the starting value of their respective group

** $P = 0.001$ versus groups 1 and 2 at the same time of observation

Severity of GO

At 6 months, proptosis decreased significantly with respect to the starting values in both groups 1 and 2 ($P = 0.001$), without any further variations during the follow-up. In group 3 proptosis decreased significantly only at 24 months ($P = 0.001$). Moreover, at 6 months the degree of diplopia significantly improved in both groups 1 ($P = 0.001$) and 2 ($P < 0.04$) with respect to baseline value. At variance, in group 3 patients, diplopia degree improved significantly only in five out of 25 patients. Instead, five patients, showing a worsening of GO during the follow-up, were excluded from the study because they required other specific treatment for GO (Table 2).

With regards to the individual behavior of GO, at 6 months during the follow-up, all but one patient in group 1, and all patients in group 2 showed an improvement in the activity and severity of GO. Instead, at this time of observation for group 3, only one out of 25 patients showed an improvement of the activity, but none of them showed an improvement of the severity; however, later in follow-up (between 12 and 24 months) 16/25 patients showed an improvement of the activity and 9/25 an improvement of the severity. Thus, considering comparatively in the three groups of patients the course of GO, the frequency of improvement in the severity of ocular parameters within 6 months and during all the subsequent follow-up was significantly greater in groups 1 and 2 than in group 3 ($P < 0.01$) without any significant difference between the first two groups. Similarly, with regards to the activity of GO at 6-month observation, the amelioration was significantly greater in groups 1 and 2 than in group 3 ($P < 0.01$) without any significant difference between the first two groups. At the end of the follow-up the percentage of patients presenting an improvement of activity was not significantly different between the three groups.

Serum antibodies

As regards to antibody behavior, TRAb decreased significantly already at 6 months both in group 1 and 2 patients, becoming negative in all but one of group 1 and in all patients in group 2 ($P = 0.01$ and $P < 0.04$, respectively, with respect to basal values). In group 3, they decreased significantly but persisted at high titers during all the follow-up span (Table 2).

G2sAb showed an early significant decrease already at 6 months with respect to their starting values in groups 1 and 2 ($P = 0.001$ and $P < 0.04$, respectively) persisting at low levels during the subsequent follow-up. Instead, in group 3 they showed a mild but not significant reduction at 12 and 24 months.

Discussion

This longitudinal study indicates that TT alone or followed by RAI is able to improve clinical and immunological aspects of GO, without significant differences between the two therapeutic procedures, but with earlier and more effective results with respect to treatment with antithyroid drugs.

The reported effects of thyroidectomy on the course of GO are still conflicting even if the beneficial effects on the control of thyroid function, avoiding the fluctuations of disease activity should be taken into account in the treatment of patients with GO [21]. The conflicting results are probably due to the different experimental design, such as the enrollment of patients, the type of ophthalmopathy, the extension of surgery, and the assessment of the ocular conditions [22, 23].

Several years ago, Marcocci et al. [24] showed that near-TT did not modify the course of GO. The lack of GO improvement could be caused by the persistence of even minimal residual thyroid, which could have a role in maintaining orbit autoimmune phenomena. Partially different results were reported by Moleti et al. [25]: they showed that near-TT alone was able to induce a decrease of CAS after a short time of follow-up, but was less effective in maintaining GO inactivity after a long time, compared with thyroidectomy followed by RAI. These authors suggest that total ablation of immunogenic thyroid remnant would lead to permanent control of orbital autoimmune process in GO.

In the present study, carried out in patients with GD and mild/moderate GO, we observed the effects of TT compared with TT plus radioiodine on severity and activity of disease over a follow-up of 2 years comparing the results to those in patients treated with methimazole. The first point emerging from our results is that in these patients, TT alone or followed by RAI, determined a significant improvement of severity and activity of GO, both in short- and in long-term observation after surgery. In addition, TRAb disappeared and G2sAb significantly decreased in all patients with improvement of activity and severity of ophthalmopathy, not only in patients in group 2 treated with TT followed by RAI, but also in those in group 1, treated with TT alone without any difference between the two groups of patients. This suggests that a minimal thyroid remnant, which may persist in patients after TT is immunologically ineffective.

An improvement of GO has been reported during the treatment with anti-thyroid drugs in same patients [25–27], thus it cannot be excluded that the improvement observed in our patients of groups 1 and 2 may be due to a recovery of hyperthyroidism rather than to ablation of shared antigens. To clarify this aspect we have compared the findings

recorded in patients with GO surgically treated with those in patients with GO submitted to methimazole therapy. Interestingly, we observed a reduction of CAS in these latter patients only at long-term (12–24 months) of follow-up, and we recorded an overlapping frequency in the improvement of the activity between all the groups only at the end of the observations. Apart from the recovery of hyperthyroidism, methimazole plays also an immunomodulatory action, resulting in a reduction of the autoimmune inflammation in GD, as previously reported [28]. On the other hand, thyroidectomy, by removing thyroid autoantigens and T- and B auto-reactive lymphocytes could be more effective than medical treatment in reducing the autoimmune process [29].

Thus, thyroidectomy could anticipate the amelioration of activity of the disease, even contributing to improve the quality of life in these patients. On the contrary, looking at the effects on the severity, the percentage of patients who ameliorated was significantly lower in methimazole group during all times of observation. According to these findings, thyroidectomy seems to be more effective than medical treatment in improving diplopia and proptosis in GO, but this is not related only to the recovery of hyperthyroidism.

Regarding antibody behavior, in patients under medical treatment, TRAb and G2sAb levels, even decreasing over time, were persistently present throughout all the follow-up, in the majority of patients. The persistence of low antibody levels in euthyroid patients medically treated could be ascribed to the presence of thyroid tissue which is a source of antigens and auto-reactive lymphocytes. On the contrary, thyroidectomy seems to lead a disappearance of the antibodies due to the removal of thyroid auto-antigens and T- and B auto-reactive lymphocytes. In conclusion, our results suggest that TT can influence the course of mild/moderate GO by anticipating the improvement, increasing the percentage of amelioration and maintaining the beneficial effects for long time, thus improving the quality of life of these patients.

Finally, in view of the similar effects observed both in group treated by TT and TT plus RAI, we did not feel that total ablation of thyroid with I131 after thyroidectomy is useful in patients with GD and GO without thyroid cancer because TT alone induces the same effects with reduced cost/benefit ratio.

References

1. B.S. Prabhakar, R.S. Bahn, T.J. Smith, Current perspective on the pathogenesis of Graves' disease and ophthalmopathy. Endocr. Rev. **24**, 802–835 (2003)
2. L. Bartalena, The dilemma of how to manage Graves' hyperthyrodism in patients with associated orbitopathy. J. Clin. Endocrinol. Metab. **96**, 592–599 (2011)
3. R.S. Bahn, A.E. Heufelder, Pathogenesis of Graves'ophthalmopathy. New Engl. J. Med. **329**, 1468–1475 (1993)
4. A. Feliciello, A. Porcellini, I. Ciullo, G. Bonavolontà, E.V. Avvedimento, G. Fenzi, Expression of thyrotropin-receptor mRNA in healthy and Graves' disease retro-orbital tissue. Lancet **342**, 337–338 (1993)
5. I.M. Wakelkamp, O. Bakker, L. Baldeschi, W.M. Wiersinga, M.F. Prummel, TSH-R expression and cytokine profile in orbital tissue of active vs. inactive Graves' ophthalmopathy patients. Clin. Endocrinol. **58**, 280–287 (2003)
6. K. Gunji, A. De Bellis, A. Wu Li, M. Yamada, S. Kubota, B. Ackrell, S. Wengrowicz, A. Bellastella, A. Bizzarro, A. Sinisi, J.R. Wall, Cloning and characterization of the novel thyroid and eye muscle shared protein G2s: autoantibodies against G2s are closely associated with ophthalmopathy in patients with Graves' hyperthyroidism. J. Clin. Endocrinol. Metab. **85**, 1641–1647 (2000)
7. M. Kaspar, C. Archibald, A. De Bellis, A. Wu Li, M. Yamada, C. Chang, G. Kahaly, J.R. Wall, Eye muscle antibodies and subtype of thyroid-associated ophthalmopathy. Thyroid **12**, 187–191 (2002)
8. T. Mizokami, M. Salvi, J.R. Wall, Eye muscle antibodies in Graves' ophthalmopathy: pathogenic or secondary epiphenomenon? J. Endocrinol. Invest. **27**, 221–229 (2004)
9. L. Bartalena, A. Pinchera, C. Marcocci, Management of Graves' ophthalmopathy: reality and perspectives. Endocr. Rev. **21**, 168–199 (2000)
10. G.J. Kahaly, O. Shimony, Y.N. Gellman, S.D. Lytton, L. Eshkar-Sebban, N. Rosenblum, E. Refaeli, S. Kassem, J. Ilany, D. Naor, Regulatory T-Cells in graves' orbitopathy: baseline findings and immunomodulation by Anti-T lymphocyte globulin. J. Clin. Endocrinol. Metab. **96**, 422–429 (2011)
11. N.A. Patwardhan, M. Moront, S. Rao, S. Rossi, L.E. Braverman, Surgery still has a role in Graves' hyperthyroidism. Surgery **114**, 1108–1113 (1993)
12. M.S. Barakate, G. Agarwal, T.S. Reeve, B. Barraclough, B. Robinson, L.W. Delbridge, Total thyroidectomy is now the preferred option for the surgical management of Graves' disease. ANZ J. Surg. **72**, 321–324 (2002)
13. L. Bartalena, M.L. Tanda, E. Piantanida, A. Lai, A. Pinchera, Relationship between management of hyperthyroidism and course of the ophthalmopathy. J. Endocrinol. Invest. **27**, 288–294 (2004)
14. R.D. Bliss, P.G. Gauger, L.W. Delbridge, Surgeon's approach to the thyroid gland: surgical anatomy and the importance of technique. World J. Surg. **24**, 891–897 (2000)
15. S.H. Acharya, A. Avenell, S. Philip, J. Burt, J.S. Bevan, P. Abraham, Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophtalmopathy: a systematic review. Clin. Endocrinol. **69**, 693–950 (2008)
16. A. Pinchera, W. Wiersinga, D. Glinoer, P. Kendall-Taylor, L. Koornneef, C. Marcocci, H. Schleusener, J. Romaldini, H. Niepominiscze, S. Nagataki, M. Izumi, Y. Inoue, J. Stockigt, J.R. Wall, F. Greenspan, D. Solomon, J. Garrity, C.A. Gorman, Classification of eye changes of Graves' disease. Thyroid **2**, 235–236 (1992)
17. M.F. Prummel, A. Bakker, W.M. Wiersinga, L. Baldeschi, M.P. Mourits, P. Kendall-Taylor, P. Perros, C. Neoh, A.J. Dickinson, J.H. Lazarus, C.M. Lane, A.E. Heufelder, G.J. Kahaly, S. Pitz, J. Orgiazzi, A. Hullo, A. Pinchera, C. Marcocci, M.S. Sartini, R. Rocchi, M. Nardi, G.E. Krassas, A. Halkias, Multi-center study on the characteristics and treatment strategies of patients with

Graves' orbitopathy: the first European group on Graves' orbitopathy experience. Eur. J. Endocrinol. **48**, 491–495 (2003)
18. L. Bartalena, L. Baldeschi, A.J. Dickinson, A. Eckstein, P. Kendall-Taylor, C. Marcocci, M.P. Mourits, P. Perros, K. Boboridis, A. Boschi, N. Currò, C. Daumerie, G.J. Kahaly, G. Krassas, C.M. Lane, J.H. Lazarus, M. Marinò, M. Nardi, C. Neoh, J. Orgiazzi, S. Pearce, A. Pinchera, S. Pitz, M. Salvi, P. Sivelli, M. Stahl, G. von Arx, W.M. Wiersinga, Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. Thyroid **18**, 281–282 (2008)
19. M.P. Mourits, M.F. Prummel, W.M. Wiersinga, L. Koornneef, Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin. Endocrinol. **47**, 9–14 (1997)
20. S. Costagliola, N.G. Morgenthaler, R. Hoermann, K. Badenhoop, J. Struck, D. Freitag, S. Poertl, W. Weglohner, J.M. Hollidt, B. Quadbeck, J.E. Dumont, P.M. Schumm-Draeger, A. Bergmann, K. Mann, G. Vassart, K.H. Usadel, Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. J. Clin. Endocrinol. Metab. **84**, 90–97 (1999)
21. B. Winsa, J. Rastad, G. Akerstrom, H. Johansson, K. Westermark, F.A. Karlsson, Retrospective evaluation of subtotal and total thyroidectomy in Graves' disease with and without endocrine ophthalmopathy. Eur. J. Endocrinol. **132**, 406–412 (1995)
22. A.P. Weetman, B.J. Harrison, Ablative or non-ablative therapy for Graves' hyperthyroidism in patients with ophthalmopathy? J. Endocrinol. Invest. **21**, 472–475 (1998)
23. L. Bartalena, C. Marcocci, A. Lai, M.L. Tanda, Graves' hyperthyroidism of recent onset and Graves' orbitopathy: to ablate or not to ablate the thyroid? J. Endocrinol. Invest. **31**, 578–581 (2008)
24. C. Marcocci, G. Bruno-Bossio, L. Manetti, M.L. Tanda, P. Miccoli, P. Iacconi, M.P. Bartolomei, M. Nardi, A. Pinchera, L. Bartalena, The course of Graves' ophthalmopathy is not influenced by near total thyroidectomy: a case-control study. Clin. Endocrinol. **51**, 503–508 (1999)
25. M. Moleti, F. Mattina, I. Salamone, M.A. Violi, C. Nucera, S. Baldari, M.G. Lo Schiavo, C. Regalbuto, F. Trimarchi, F. Vermiglio, Effects of thyroidectomy alone or followed by radioiodine ablation of thyroid remnants on the outcome of Graves' ophthalmopathy. Thyroid **13**, 653–658 (2003)
26. P. Perros, P. Kendall-Taylor, Natural history of thyroid eye disease. Thyroid **8**, 423–425 (1998)
27. L. Bartalena, M.L. Tanda, Clinical practice. Graves' ophthalmopathy. N. Engl. J. Med. **360**, 994–1001 (2009)
28. A. Antonelli, M. Rotondi, P. Fallahi, S.M. Ferrari, L. Barani, E. Ferranini, M. Serio, Increase of interferon-$^{\#}$-inducible CXC chemokine CXCL10 serum levels in patients with active Graves' disease, and modulation by methimazole therapy. Clin. Endocrinol. **64**, 189–195 (2006)
29. A. Antonelli, P. Fallahi, M. Rotondi, S.M. Ferrari, M. Serio, P. Miccoli, Serum levels of the interferon-gamma-inducible alpha chemokine CXCL10 in patients with active Graves' disease, and modulation by methimazole therapy and thyroidectomy. Br. J. Surg. **93**, 1226–1231 (2006)