Clinical Thyroidology / Original Paper

European
Thyroid Journal

Eur Thyroid J 2016;5:106–111
DOI: 10.1159/000444796

Received: December 14, 2015
Accepted after revision: February 16, 2016
Published online: April 26, 2016

Comparison of Early Total Thyroidectomy with Antithyroid Treatment in Patients with Moderate-Severe Graves' Orbitopathy: A Randomized Prospective Trial

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Key Words
Antithyroid treatment · Graves' orbitopathy · Total thyroidectomy

Abstract
Background: The optimal therapeutic choice for Graves' hyperthyroidism in the presence of moderate-severe Graves' orbitopathy (GO) remains controversial. ***Objectives:*** We aimed to compare GO course in patients with moderate-severe GO treated with early total thyroidectomy (TTx) versus antithyroid drug (ATD) regimens, in a prospective, randomized manner. ***Methods:*** Forty-two patients with moderate-severe GO were enrolled. A total of 4.5 g of pulse corticosteroids were given intravenously to all patients before randomization. Patients in the first group were given TTx, whereas patients in the second group were treated with ATDs. TSH was kept between 0.4 and 1 mIU/l. The clinical course of GO was evaluated with proptosis, lid aperture, clinical activity score (CAS), and diplopia. ***Results:*** Eighteen and 24 patients were randomized to the TTx and ATD groups, respectively. Thyroid autoantibodies decreased significantly, and there were significant improvements in proptosis, lid aperture, and CAS in the TTx group. While in the ATD group the decrement in thyroid autoantibodies was not significant, there were significant improvements in proptosis and CAS. When the TTx group was compared with the ATD group, anti-TPO, anti-Tg, and TSH-receptor antibodies were significantly decreased in the TTx group ($p < 0.01$), but there was no significant difference with respect to proptosis, lid aperture, CAS, and diplopia between the two groups during a median (min.–max.) follow-up period of 60 months (36–72). ***Conclusion:*** Although no definitive conclusions could be drawn from the study, mainly due to limited power, early TTx and the ATD treatment regimens, followed by intravenous

Clinical Trial Registration No.: NCT01056419

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pulse corticosteroid therapy, seemed to be equally effective on the course of GO in this relatively small group of patients with moderate-severe GO during a median (min.–max.) follow-up period of 60 months (36–72).

Introduction

Graves' orbitopathy (GO) is a devastating and disfiguring disease affecting appearance and functioning of the eyes and thus profoundly impairing the quality of life of affected individuals [1]. GO is an autoimmune disorder, but its precise pathogenic mechanisms are not fully known [2, 3]. Autoimmunity in the orbital space is likely to be triggered by autoreactive T lymphocytes reaching the orbita and recognizing one or more antigens (the TSH receptor; IGF-1 receptor) shared by the thyroid and the orbita and presented by antigen-presenting cells, including B lymphocytes [2, 3]. The subsequent cascade of events, including secretion of a number of cytokines, causes expansion of the orbital fibroadipose tissue, infiltration, and enlargement of extraocular muscles [2, 3]. These changes are mechanically responsible for the clinical manifestations of GO, including exophthalmos, extraocular muscle dysfunction, causing diplopia, ocular soft tissue changes, and optic nerve compression [4].

Based on the above pathogenic model, thyroid disease could be responsible for the occurrence of GO; therefore, reduction of thyroid tissue either by radioiodine or total thyroidectomy (TTx) might deplete autoreactive T lymphocytes and thereby be beneficial for the clinical course of GO. On the other hand, it can be argued that once autoimmunity is triggered and GO is clinically overt, its course and treatment might be unaltered by thyroid ablation. In this case, antithyroid drug (ATD) treatment might be preferable. Evidence based on randomized clinical trials in this field is scant [4]. Thus, the choice of optimal treatment regarding thyrotoxicosis in patients with moderate-severe GO is a matter of debate. It is well known that pretreatment variables such as ethnicity, sex, age, severe thyrotoxicosis, higher serum levels of TSH-receptor antibodies (TRAbs), and smoking do influence response to therapy. Restoring euthyroidism and abstaining from smoking are the most important management goals [5, 6].

Aim of the Study

We aimed to compare GO course in patients with moderate-severe GO treated with early TTx versus ATD regimens in a prospective randomized manner.

Patients and Methods

Patient enrollment for the study was started in November 2008. Sixty-two GO patients were referred from different endocrinology clinics in Ankara, and 42 patients with moderate-severe GO who fulfilled the following criteria were enrolled:

1 Hyperthyroidism and GO developed in the last 6 months
2 Thyroid volume ≥15 ml
3 No previous treatment except local interventions for GO
4 GO activity defined as clinical activity score (CAS) ≥3 and carrying at least one of the following criteria: proptosis ≥21 mm in one eye, ≥2 mm difference in Hertel measurements between two eyes, presence of diplopia, and lid aperture ≥9 mm

Diplopia was defined as constant, in primary position and in gaze positions. All the patients were moderate to severely active cases (i.e. CAS ≥3).

Smoking habits and family history of GO were noted. Thyroid ultrasonography was performed for the determination of thyroid volume and nodularity. Nodules were biopsied when necessary. Assessment of activity was done with CAS, which includes 7 items (eyelid edema, eyelid erythema, conjunctival redness, chemosis, edema of the caruncle, spontaneous ocular pain, and pain with ocular movements). Proptosis with a Hertel-meter, lid aperture, and diplopia were evaluated by the same experienced endocrinologist and the patients were only referred to the ophthalmologist when it was necessary. TSH, free T_4, TRAb, anti-TPO, and anti-Tg levels were measured in 4-week to 3- and 6-month intervals during follow-up.

All the patients were treated with ATDs until euthyroidism was reached and TSH levels were kept within the range of 0.4–1 mIU/l. Initial CAS was established before euthyroidism was reached and also before intravenous pulse therapy had been initiated in all of the patients. The average time of euthyroidism was 6 weeks after enrolment. Pulse corticosteroids (methylprednisolone) 500 mg i.v. twice weekly, for 3 weeks, followed by 250 mg twice weekly, for 3 weeks, reaching a total of 4.5 g in 6 weeks were given to all patients before randomization. Immediately after the completion of the pulse corticosteroids, patients were randomized to two groups. One-to-one randomization rules were obeyed; however, 3 patients refused TTx and were enrolled in the ATD group instead of the TTx group. Patients were sent to TTx and their TSH levels were kept within the range of 0.4–1 mIU/l with levothyroxine replacement, starting early after surgery. The second group was the ATD group, where the patients were followed with ATDs and with the addition of levothyroxine, when necessary, to keep TSH within the range of 0.4–1 mIU/l. All patients completed 36 months of follow-up, with a median (min.–max.) of 60 months (36–72).

Ethical approval was obtained from the local ethics committee of Ufuk University, Ankara.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 20.0 (IBM Corp, Armonk, N.Y., USA). Categorical data were compared using the χ^2 Fisher's exact test. Group data with a normal distribution were compared using Student's t test or analysis of variance. A Mann-Whitney U test and Wilcoxon signed-rank test were used appropriately to compare inter-/intragroup nonparametric data. Friedman's test was used to explore the changes in ordinal and continuous variables during follow-up in each treatment group. Changes in dichotomous variables were evaluated with McNemar's test. Values were expressed as means ± SD or medians as appropriate. $p < 0.05$ was considered statistically significant.

Table 1. Comparison of the initial parameters in patients treated with early TTx and the ATD regimens

	TTx	ATD	p
Patients	18	24	–
Follow-up period, months	60 (36–72)	60 (36–72)	–
Age[a], years	44±8.7	35±12.9	0.09
Gender[b], male/female	7/11	12/12	0.39
Cigarette smoking[c], pack-years	9.4	6.9	0.58
Duration of hyperthyroidism[c], months	6 (1–6)	6 (1–6)	0.67
Duration of orbitopathy[c], months	4.5 (1–6)	5 (1–6)	0.87
Thyroid volume[a], ml	27.8±12.55	28.99±12.59	0.80
TSH[d] (0.34–5.6 μIU/ml)	0.05 (0.01–1.4)	0.3 (0.005–1.8)	0.86
Free T_4[d] (7–16 pmol/l)	15.7 (11.2–59.9)	13.8 (7.6–61)	0.29
Anti-TPO[d] (0–9 kU/l)	379 (10–1,097)	319 (7–1,300)	0.49
Anti-Tg[d] (0–4 kU/l)	552 (1–2,682)	113 (1–2,654)	0.51
TRAb[d] (0–9 U/l)	37.2 (0.2-675)	7.4 (2–472)	0.08

Values are given as n, medians (min.–max.) or means ± SD. [a] t test. [b] χ^2 test. [c] Mann-Whitney test. [d] Wilcoxon signed-ranks test.

Results

Eighteen patients were randomized to the TTx group and 24 patients were randomized to the ATD group. One-to-one randomization rules were obeyed; however, a few patients refused TTx and were put in the ATD group. Initially, there were no differences between the two groups with respect to age, gender, smoking habits, duration of hyperthyroidism and GO, thyroid volume, and serum levels of the parameters studied (table 1).

During a median 60 months of follow-up, thyroid autoantibodies decreased significantly, and there were significant improvements in proptosis, lid aperture, and CAS for the TTx group. However, no improvement was reported in diplopia for this group (table 2). While in the ATD group the decrement in thyroid autoantibodies was not significant, there were statistically significant improvements in proptosis and CAS. Lid aperture and diplopia did not change significantly (table 2).

When the TTx group was compared with the ATD group, anti-TPO, anti-Tg, and TRAb were significantly decreased in the TTx group while there was no significant difference with respect to proptosis, lid aperture, CAS, and diplopia between the two groups during a median follow-up period of 60 months (table 3).

Additional intravenous pulse corticosteroid treatment was necessary in 3 patients in the TTx group and urgent orbital decompression was applied to 2 of these patients. Patient 1 was a 49-year-old male, and micropapillary thyroid carcinoma was detected after surgery. Radioiodine was neither indicated nor given, but severe activation of GO occurred 3 months after surgery. Additional pulse corticosteroid treatment was given, reaching a total of 12 g. Urgent orbital decompression was performed due to dysthyroid optic neuropathy. Patient 2 was a 41-year-old female. Micropapillary thyroid carcinoma was also detected after surgery. Radioiodine was neither indicated nor given; however, activation of GO occurred approximately 3 months after surgery. Additional pulse corticosteroid treatment was also given when necessary (total: 12 g) and urgent orbital decompression was applied due to dysthyroid optic neuropathy. Patient 3 was a 49-year-old female. Activation of GO occurred approximately 3 months after surgery. Additional pulse corticosteroid treatment was given (total: 12 g) due to severe eye involvement, but could be stabilized without orbital decompression.

Hyperthyroidism reoccurred in 3 patients from the ATD group, early after discontinuation of ATD treatment for 18–24 months, and ATDs were reinitiated.

Discussion

Management of GO is based on three pillars: ceasing smoking, treating the eye changes according to severity and activity, and restoring and maintaining euthyroidism. In the presence of moderate-severe GO, patients should receive prompt therapy since treatment outcome is inversely correlated to disease duration [7]. The steroid treatment should be used for active cases as a first-line treatment [7].

Table 2. Course of thyroid autoantibodies (anti-TPO, anti-Tg, TRAb), proptosis, lid aperture, CAS, and diplopia in the study groups

	0	6 months	12 months	24 months	36 months	p
TTx (n = 18)						
Anti-TPO (0–9 kU/l)	379	89[a]	51[a]	38[a]	33[a]	<0.001
Anti-Tg (0–4 kU/l)	553	100[a]	67[a]	42[a]	36[a]	<0.001
TRAb (0–9 U/l)	80	22	17[a]	15[a]	13[a]	<0.01
Proptosis						
Right	19.5	18.3	18.1[a]	18.0[a]	18.0[a]	<0.05
Left	20.1	18.5[a]	18.6[a]	18.3[a]	18.2[a]	<0.05
Lid aperture						
Right	11.6	10.2	10.3[a]	10.0[a]	10.0[a]	<0.05
Left	11.8	11.0	10.9[a]	10.3[a]	10.3[a]	0.05
CAS	4	1.5	1[a]	1	1	<0.001
Diplopia, n	6	3	3	3	3	>0.05
ATD (n = 24)						
Anti-TPO (0–9 kU/l)	319	213	188	185	185	>0.05
Anti-Tg (0–4 kU/l)	113	67	54	54	54	>0.05
TRAb (0–9 U/l)	54	16	16	16	16	>0.05
Proptosis						
Right	19.1	17.9[a]	17.7[a]	17.6[a]	17.5[a]	<0.05
Left	19.2	18.1[a]	18.1[a]	18.01[a]	18.0[a]	<0.05
Lid aperture						
Right	11.8	11.2	11.1	11.0	11.1	>0.05
Left	12.6	11.6	11.6	11.6	11.6	>0.05
CAS	3	0[a]	0[a]	0[a]	0[a]	<0.001
Diplopia, n	3	1	1	1	1	>0.05

[a] Point where statistical significance was reached.

Table 3. Comparison of the change in study parameters for patients treated with early TTx versus those who received ATD treatment at the median follow-up time of 60 months

	TTx	ATD	p
ΔProptosis[a]	–0.5	–1	>0.05
ΔCAS[a]	–2	–2	>0.05
ΔLid aperture[a]	0	0	>0.05
ΔDiplopia[b]	–1	–2	>0.05
ΔAnti-TPO[a], kU/l	–90	0	0.009
ΔAnti-Tg[a], kU/l	–96	–42	0.05
ΔTRAb[a], U/l	–79	0	0.05

[1] Mann-Whitney test. [b] χ^2 test.

Controversy exists on the most appropriate treatment of hyperthyroidism in the presence of moderate-severe GO. Since radioiodine may worsen the GO course, TTx or long-term (18–24 months) treatment with ATDs are the treatment options. However, evidence demonstrating the superiority of one over the other in a prospective randomized manner is lacking [8].

In a prospective case-control study, near TTx and ATDs were not associated with significant ocular changes in patients with nonsevere/absent GO who were followed for 12 months [9]. Conversely, in a prospective trial of 48 patients, GO improved after surgery in 90% of the patients [10]. In a study by Tanda et al. [11] with 237 patients who completed an 18-month follow-up period, only 6.1% had moderate-severe GO initially. Progression to moderate-severe GO occurred in 2.6% of the patients who had no GO at baseline, whereas 2.4% of the patients with mild and inactive GO at baseline progressed to moderate-severe GO during follow-up under ATDs. Thus, the effect of ATDs on the course of GO seems to be neutral. In a randomized control trial comparing radioiodine and ATDs, most patients had stable ocular conditions during ATD treatment, few (3%) progressed, and few (2%) remitted, in accordance with the natural history of GO [12].

ATDs may, however, have an indirect, beneficial effect on GO, related to control of hyperthyroidism [13], and/or gradual decrease in TRAb levels during treatment [14, 15]. Tallstedt et al. [16] showed that the frequency of new development or progression of GO among patients submitted to subtotal thyroidectomy or treated with ATDs did not differ significantly.

While not supported by randomized clinical trials, an important argument in favor of ATD treatment is that prompt correction of hyperthyroidism and maintenance of euthyroidism (if well titrated or block-replace regimens are used), which is beneficial for GO, are usually achieved [13]. In general, patients with GO can be treated with ATDs, which is a safe way to maintain euthyroidism. In this manner, definitive treatment for hyperthyroidism, if needed, could be postponed after inactivation and/or remission of GO [17, 18]. On the other hand, ATD treatment is associated with a high relapse rate after drug withdrawal [19], and the continuing thyroid hyperactivity and fluctuations in thyroid hormone and TSH serum levels, during or after ATD treatment might negatively influence the course of GO. Thus, after control of hyperthyroidism with ATD, the thyroid could be surgically ablated while GO is concomitantly managed with pulse corticosteroids [20–24]. Currently, evidence is scant for the superiority of the conservative approach over the surgical approach or vice versa [25]. Thus, in patients with moderate-severe GO, active treatment for GO with pulse corticosteroids is warranted; however, treatment options for hyperthyroidism are largely based on expert opinion and clinical experience rather than evidence [26–28].

To our knowledge, this study is the only one that has compared the moderate-severe GO course in patients treated with early TTx and ATD regimens in a randomized prospective manner. Both of the treatment regimens (i.e. TTx vs. ATD) seemed to be equally effective on the course of GO after pulse corticosteroid therapy. Although a significant decrease of thyroid autoantibodies was achieved in the TTx group, this was not reflected as a beneficial effect on the course of GO during a median follow-up period of 60 months (36–72). Nevertheless, it is important to note that additional corticosteroid pulses were mandatory for 3 patients, of whom 2 had been referred to orbital decompression, from the TTx group. These 3 patients had similar CAS and GO risk factors when compared with the remaining patients initially. Up to now, hyperthyroidism reoccurred in 3 of 24 patients (12.5%) in the ATD group, after 18–24 months of treatment.

There were some limitations to the current study. Firstly, the number of patients enrolled in each group was insufficient, decreasing the power of the study. In reality and fortunately, clinical manifestations of patients with GO are changing in Europe and probably elsewhere, and mild and inactive GO are becoming more prevalent [29]. Each year we encounter fewer moderate-severe GO cases. Accordingly, it is difficult to enroll patients, even in a multicenter setting. Secondly, our intravenous pulse corticosteroid protocol is a modified one, doubling the doses in the first 3 weeks as described above, although the final total doses are comparable to other studies (i.e. 4.5–6 g/day). Yet, it seemed to be equally effective with the standard longer protocol and none of our patients experienced any important side effects.

Conclusion

Although no definitive conclusions can be drawn from the study, mainly due to limited power, early TTx and ATD treatment regimens followed by intravenous pulse corticosteroid therapy seemed to be equally effective on the course of GO in this relatively small group of patients with moderate-severe GO during a median (min.–max.) follow-up period of 60 months (36–72).

Disclosure Statement

There is no conflict of interest for each author and there is no source of any support for the study.

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