

Determinants of Favourable Outcome Among Adults with Active Thyroid Eye Disease: The Remarkable Role of Long-Duration Treatment Approaches

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Abstract: *Background:* The response to treatment in adult patients suffering from thyroid-eye-disease is variable, with resistant and relapsing cases. Clinical and therapeutic factors involved are not well established. *Objectives:* To identify clinical determinants of favourable outcome in a sample of adults with active thyroid orbitopathy who received multidisciplinary treatment and to evaluate the effect of long duration treatment approaches for moderate-to-severe cases. *Methods:* This retrospective observational study included patients treated in a hospital environment with a follow-up of more than 1 year. The criteria for a favourable outcome after treatment were a final Clinic Activity Score (CAS) < 2 and fewer than 3 posttreatment visits with a CAS > 1. The treatments used for moderate-to-severe orbitopathy were categorized according to duration. The following were considered long-duration treatments (LDTs): radiotherapy combined with intravenous corticosteroids; and tocilizumab. These LDTs were compared with treatments that were administered for up to 3 months. Fisher's and Mann-Whitney tests were used to verify relationships between qualitative and quantitative variables. Logistic and linear regressions were used to predict dichotomous and numerical variables. *Results:* Seventy-two patients were included in the study. Active smoking and sustained endocrine disease were associated with a longer duration of active orbitopathy ($p = 0.045$ and $p < 0.001$, respectively). Radioiodine-induced hypothyroidism and arterial hypertension were negatively correlated with a favourable outcome event, with ORs of 0.12 ($p = 0.008$) and 0.16 ($p = 0.019$), respectively. LDTs were determinants of favourable outcome, with an odds ratio of 6.85 ($p = 0.015$). LDTs also led to a greater decrease in the CAS ($p = 0.03$). *Conclusion:* Active smoking, radioiodine-induced hypothyroidism, arterial hypertension, and sustained endocrine disease are associated with non-favourable outcome after treatment. LDTs contribute to favourable outcomes in adult patients with active moderate-to severe thyroid ophthalmopathy.

Keywords: Thyroid Orbitopathy, Thyroid-Associated Ophthalmopathy, Graves' Disease, Thyroid-Eye-Disease, Outcome Determinants, Duration of Treatment

1. Introduction

Thyroid-associated ophthalmopathy or thyroid-eye-disease (TED) is an orbital and ocular disease resulting from a complex immunological disorder, generally within the context of hyperthyroidism in Graves' disease or autoimmune thyroiditis [1]. The association between orbitopathy and hyperthyroidism suggests that these pathologies share autoantigens [2].

The active or inflammatory phase of TED is characterized by pain and inflammatory signs that primarily affect periocular structures. Despite the use of appropriate treatments, the duration of TED is variable and not well established.

Several factors are known to exacerbate the evolution of orbitopathy in adequately treated patients. Smoking increases the frequency and severity of orbitopathy in hyperthyroid patients and increases resistance to treatment [3]. Similarly, elevated levels of TSH-binding inhibitory immunoglobulins, elevated levels of LDL cholesterol, a longer duration of hyperthyroidism and the appearance of radioiodine-induced hypothyroidism are determinants of worse treatment outcomes [1, 4].

To reduce the inflammation, characteristic of the active phase of TED, multiple treatment options have been proposed. However, despite being a self-limited process, there are cases that qualify as resistant. These are cases in which treatment fails to attenuate the severity or reduce the duration of the active disease phase to tolerable levels.

Selenium supplementation (sodium selenite, 200 µg) has been shown to improve the course of mild TED when it is used daily for 6 months. This treatment is rarely used in more advanced stages because there is no evidence of a beneficial effect [5].

Corticosteroids have been the basis of treatment for many years, but long-term administration can result in serious adverse effects.

Radiation therapy has more long-lasting action; however, radiation alone does not offer better results than corticosteroids, and the effects are notably delayed [6]. Low radiation doses (10 Gy) fractionated into 1 Gy per week over 10 weeks, have been shown to be effective for treating TED. Moreover, new radiation techniques, such as volumetric modulated arc therapy (VMAT), can be used to minimize damage to adjacent tissue [7].

Finally, several biological agents have been shown to be effective as second lines of treatment. Teprotumumab has become the first drug approved by the U.S. Food and Drug Administration for the treatment of adult GO. However, tocilizumab and rituximab have been more widely used in our region (Spain).

The objective of this study was to identify the clinical determinants of favourable evolution, in a sample of adult patients with active TED who received specific and multidisciplinary treatment in our hospital. We also evaluated the effect of long-duration treatments in the subset of patients

with active moderate-to-severe TED.

2. Materials and Methods

2.1. Study Design

This retrospective observational study was conducted at the University Hospital of Gran Canaria Doctor Negrín (Canary Islands, Spain) and was approved by the hospital ethics committee. We examined records from all adult patients who presented with active TED and were treated at a specialized hospital department, between 2017 and 2022.

The inclusion criteria were as follows: active TED (mild or moderate to severe, as defined by the European Group on Graves' Orbitopathy [EUGOGO]) [4]; relevant computerized tomography scans (revealing exophthalmos or involvement of extraocular muscles); complete endocrine and ophthalmic evaluation and management (provided by endocrinology and ophthalmology experts); and a follow-up period of more than 1 year (at least 5 posttreatment visits). The exclusion criteria were as follows: patients who did not require specific ophthalmological treatment, patients who needed only local treatments, and patients who refused all proposed treatments.

Active TED was assessed using the clinical activity score (CAS) in accordance with the recommendations of the EUGOGO [8].

The following parameters were extracted from the clinical records: sex, presence of overweight or obesity, smoking status, personal history of arterial hypertension (AHT), personal history of diabetes mellitus, radioiodine-induced hypothyroidism, laterality of orbital disease, age at onset of endocrine disease, age at onset of orbitopathy, duration of endocrine disease (in case of relapse, the joint duration of all was considered); duration of active orbitopathy (active orbitopathy was considered resolved [end of active TED] when achieving and maintaining a CAS < 3 in the remainder of follow-up visits); duration of the follow-up period; "ophthalmic treatment" (for different or additional treatments, only the one that provided the most durable improvement was considered); changes in ophthalmic treatment (number of additional treatments after the first treatment); initial CAS (pretreatment values); final CAS (average CAS for different post treatment visits); and number of post treatment visits in which the CAS was > 1. A favourable outcome was defined as a final CAS < 2 and fewer than three posttreatment visits with a CAS > 1.

The following treatment approaches were considered to be long-duration treatments (LDTs) for active moderate-to-severe TED: radiotherapy combined with intravenous corticosteroids (longer-lasting action is observed when these treatments are used in combination than when they are used separately); and tocilizumab (for which the duration can be adjusted based on the response).

Conversely, oral corticosteroids, isolated intravenous corticosteroids (12 weeks of treatment) and isolated radiotherapy (which leads to a shorter-lasting effect than

when it is combined with corticosteroids) were not considered LDTs. Selenium supplementation is used only for mild active TED and was not included herein.

2.2. Procedures

Selenium supplementation was prescribed for six months exclusively for patients with mild active TED.

Concerning moderate to severe orbitopathy, oral corticosteroids, methotrexate, azathioprine and cyclosporine were rarely used. In our hands, these agents exhibit early toxicity and low efficacy, suggesting the need for additional treatments. Therefore, they had low or no impact on this study.

Intravenous corticosteroids were administered as follows: 0.5 g of methylprednisolone weekly for 6 weeks, followed by 0.25 g of methylprednisolone weekly for 6 additional weeks, for a cumulative dose of 4.5 g.

Radiotherapy was performed using volumetric modulated arc therapy, with a total absorbed dose of 10 Gy fractionated at 1 Gy once per week over 10 weeks.

The combined treatment included both glucocorticoids and radiotherapy over 12 weeks. In the first 10 weeks, both treatments were scheduled for the same day of the week; in the following two weeks, patients received intravenous methylprednisolone alone. It was used mainly as a first-line treatment, as well as a second-line treatment when other options failed.

Tocilizumab was always used as an additional treatment (second-line treatment) at a dosage of 8 mg/kg of weight via monthly intravenous injections for 4 to 8 months.

2.3. Statistical Analysis

The statistical analysis was performed using R Core Team 2023 (version 4.3.1).

The determinants of a favourable outcome were identified

using Fisher's exact test and a logistic regression model. To evaluate the efficacy of long-duration treatment approaches, a new logistic regression model that included this variable was generated for the subset of patients suffering from moderate-to-severe TED.

Determinants related to the duration of active TED were identified using multiple linear regression. In addition, the duration of active orbitopathy was compared in subgroups of patients who presented possible determinant factors using the nonparametric Mann Whitney test. Patients who did not achieve and maintain a CAS < 3 during the follow-up period (i.e., orbitopathy was active at the end of the follow-up period) were excluded from these comparisons.

Finally, the evolution of the CAS was compared between patients who received long-duration treatment approaches and those who did not.

3. Results

3.1. Descriptive Analysis

After the application of the aforementioned inclusion and exclusion criteria, the data of 72 patients (55 women and 17 men) were included in the study. Table 1 summarizes the variables of the patients included. Fifty-four patients suffered from moderate-to-severe TED, and in this subset, 34 (63%) patients received LDTs. The following “ophthalmic treatments” were applied: selenium supplementation for 18 patients, oral corticosteroids for 4 patients, intravenous corticosteroids for 10 patients, radiotherapy for 6 patients, radiotherapy combined with intravenous corticosteroids for 29 patients and tocilizumab for 5 patients. A favourable outcome, as defined herein, was achieved in 41 patients in the overall (57%) and in 25 patients with moderate-to-severe TED (46%).

Table 1. Description of the quantitative and qualitative variables.

Quantitative variables:	Whole sample (N=72)*		M-S subset (N=54)
	MEAN (SD)	MEDIAN (P25 - P75)	MEDIAN (P25 - P75)
Age at endocrine disease onset	47.8 years (12.6)	48 (37.5 – 54.5)	46.5 (36.7 – 53)
Age at thyroid orbitopathy onset	51.2 years (11.9)	49 (43.5 – 57)	50 (43 – 56)
Duration of endocrine disease	3.6 years (4.7)	2 (1 – 4)	2 (1 – 4)
Duration of active orbitopathy	44.27 months (30.29)	33 (22 – 68)	28 (21.5 – 64)
Follow-up	53.31 months (30.37)	50 (27.7 – 72)	51 (27.2 – 72)
Changes in ophthalmic treatment	1 (1.2)	1 (0 – 1.2)	1 (0 – 2.7)
Initial CAS	3.24 (1.1)	3 (3 – 4)	3 (3 – 4)
Final CAS	1.19 (0.8)	1 (1 – 2)	1 (1 – 2)
Post treatment visits with CAS>1	1.54 (1.4)	1.5 (0 – 2)	2 (0 – 3)
Qualitative variables:		Frequencies:	Frequencies:
Active smoker		41 (57%)	30 (56%)
Radioiodine-induced hypothyroidism		34 (48%)	25 (46%)
Arterial hypertension		31 (43%)	23 (43%)
Diabetes mellitus		13 (18%)	9 (17%)
Obesity		27 (38%)	19 (35%)
Grave's disease		62 (86%)	48 (89%)
Other thyroid diseases/status		10 (14%)	6 (11%)
Concomitant autoimmune diseases (alopecia, myasthenia, others)		18 (25%)	13 (24%)
Unilateral orbitopathy		10 (14%)	10 (19%)

*N = 72 except for “duration of active orbitopathy”, where only patients who reached a sustained CAS < 3 after treatment were considered (n = 55) (Abbreviations: SD = standard deviation; P25 = first quartile; P75 = third quartile; M-S subset = subset of patients with moderate-to-severe orbitopathy).

3.2. Comparisons Regarding the Parameter Favourable Outcome

Tables 2 and 3 provide the results of the multivariate analysis for the whole sample and for the subset of patients with moderate-to-severe TED, respectively. A personal history of AHT, radioiodine-induced hypothyroidism and, in

the subset of patients with moderate-to-severe TED, the use of LDTs were determinants of a favourable outcome. Additionally, when we focused on this subset of patients and performed Fisher's exact test, the odds ratio for achieving a favourable outcome in patients treated with LDTs was 5.62 (confidence interval 95%: 1.54 to 20.51 and $p=0.008$).

Table 2. Determinants of a favourable outcome in the whole sample, identified using multivariable analysis.

Variable	Multivariable analysis (Optimal model)			Bootstrapping (Optimal model)	
	OR	CI (95%)	p value	OR	CI (95%)
(Intercept)	0.184	0.059 to 0.475	0.001	0.195	0.065 to 0.516
AHT	4.297	1.478 to 13.895	0.01	4.058	1.27 to 14.644
Radioiodine-induced hypothyroidism	4.13	1.427 to 13.357	0.012	3.898	1.25 to 14.614
AUROC	0.724			-	

The event of study was "not to achieve favourable outcomes". The presence of arterial hypertension or radioiodine-induced hypothyroidism hinders a favourable outcome. OR = odds ratio; * = statistically significant. CI = confidence interval. AHT= arterial hypertension. AUROC = area under the ROC curve

Table 3. Determinants of a favourable outcome in the moderate to severe subset identified using multivariate analysis.

Variable	Multivariable analysis (Optimum model)			Bootstrapping (Optimum model)	
	OR	CI (95%)	p value	OR	CI (95%)
(Intercept)	1.638	0.329 to 9.212	0.547	1.514	0 to 16.851
LDTs	6.853	1.59 to 38.054	0.015*	5.672	0.938 to 40.764
AHT	0.156	0.027 to 0.67	0.019*	0.186	0.022 to 1.33
Radioiodine-induced hypothyroidism	0.117	0.02 to 0.497	0.008*	0.14	0.018 to 0.819
AUROC	0.834			-	

The event of study was "to achieve favourable outcome". Long-duration treatment promotes favourable outcomes (odds ratio > 1), and the presence of arterial hypertension or radioiodine-induced hypothyroidism hinders favourable outcomes (odds ratio <1). Abbreviations as above.

Homogeneity tests: Comparisons among groups with and without AHT, radioiodine-induced hypothyroidism, active smoking and LDTs while controlling for baseline characteristics and initial CAS did not reveal significant differences.

3.3. Comparisons Regarding the Parameter "Duration of Active Orbitopathy"

As a determinant of the duration of active orbitopathy,

active smoking increased the duration of active orbitopathy in the whole sample, whereas the use of LDTs decreased the duration of active orbitopathy in patients with moderate-to-severe TED (Table 4). Table 5 shows the optimal model for predicting the duration of active orbitopathy, in which only the use of LDT had predictive value ($p = 0.01$). A notable correlation was also found between the duration of thyroid disease and the duration of the active phase of orbitopathy (Figure 1).

Table 4. Duration of active orbitopathy, comparing the group of active smokers to nonsmokers (whole sample) and the group that received long-duration treatment with the group that did not (subset of patients with moderate to severe orbitopathy).

Group	N	Duration of active orbitopathy (months) Median (P25 – P75)	Mann Whitney test
Active smokers	25	37.5 (25.2 – 74.7)	
Non active smokers	30	27 (14 – 52)	P= 0.045 *
LTDs (M-S subset)	27	25 (19.5-38.5)	
Non LTDs (M-S subset)	16	66 (40 – 74)	P= 0.003 *

The absence of active smoking and long duration treatments are associated with a shorter duration of active orbitopathy. Note that only patients who met the criteria for "end of orbitopathy" were included in the analysis (55 patients in the whole sample and 43 in the M-S subset). LTDs = long duration treatments; * = statistically significant; M-S subset = subset of patients with moderate-to severe orbitopathy

Table 5. Optimal model for predicting the duration of active orbitopathy according to multiple linear regression.

Variable	Multiple linear regression (Optimal model)					Bootstrapping (Optimal model)	
	β	EE	B	CI (95%)	P value	β	CI (95%)
(Intercept)	63.333	7.911	-	47.42 to 79.25	<000.1	63.2	49.485 to 73.857
LDTs	-24.306	9.104	-0.36	-42.62 to -5.99	0.01	-24.04	-38.15 to -8

The use of LDTs reduced the mean duration of active orbitopathy by > 24 months and was the only significant variable. CI = confidence interval

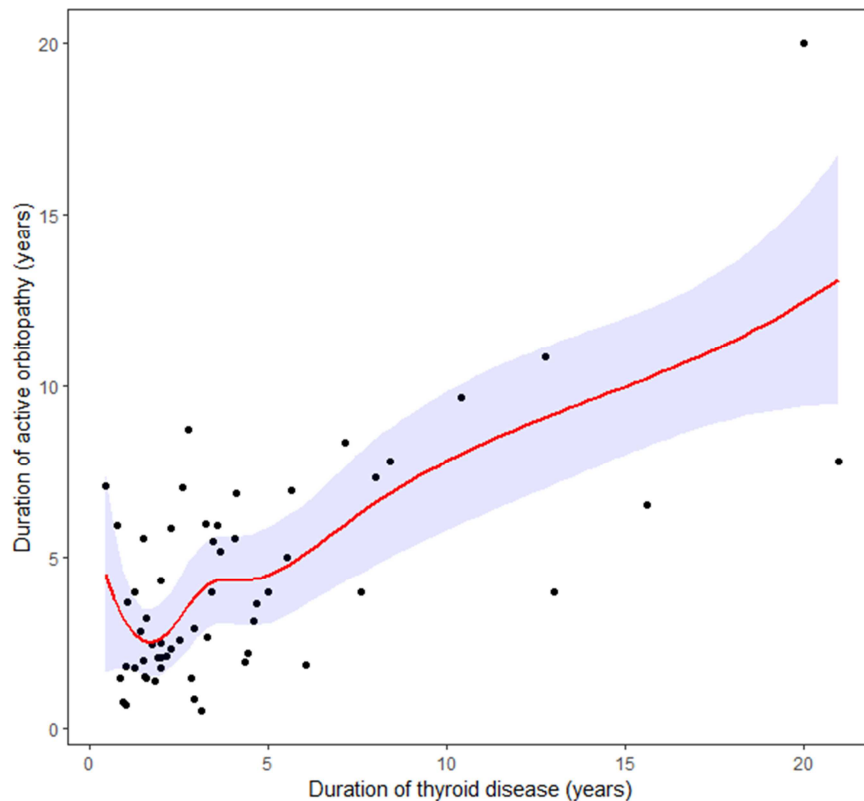


Figure 1. Regression line showing the relationship between the duration of endocrine disorder (hyperthyroidism) and the duration of active orbitopathy. The Pearson correlation coefficient (r -value) was 0.68 (95% CI 0.51 to 0.79, $p > 0.01$), and the Spearman correlation coefficient (r -value) was 0.53 ($p < 0.001$). Only patients who met the criteria for “end of orbitopathy” were considered.

3.4. Comparisons with Respect to CAS

Once again, only the use of LDTs was associated with more favourable responses, with a lower final CAS and a greater decrease in CAS as a result of treatment (Table 6).

Table 6. Comparison of the initial, final, and decrease in CAS (initial CAS – final CAS) between the group that did not receive LDTs and the group that did.

Variable	Non LDTs (n=20)	LDT (n=34)	Mann Whitney test
Initial CAS: Median (P25 – P75)	3 (3 – 4)	3 (3 – 4)	P=0.28
Final CAS: Median (P25 – P75)	2 (1 – 2)	1 (1 – 1.5)	P=0.009 *
Decrease in CAS: Median (P25 – P75)	2 (1 – 2)	3 (2 – 3)	P=0.003 *

The use of LDTs was associated with more favourable results, with a lower final CAS and a greater decrease in CAS. LDTs = long duration treatments, * = statistically significant

4. Discussion

In this study, we sought to identify the clinical factors that determine a more favourable evolution of active TED in adult patients who received multidisciplinary treatment between 2017 and 2022 in our hospital. Improvement and stability of CAS were assessed to define favourable evolution, with favourable outcome pertaining only to those patients with scores less than 2 at posttreatment visits. Other changes, such as a reduction in exophthalmos or improvement in motility, were not considered because they reflect inflammatory activity in a more indirect way and because the

values of these measures do not usually return to normal until rehabilitative surgery is performed.

The long duration of hyperthyroidism and TED in our patients was noteworthy (Table 1 and Figure 1). It is possible that numerous patients refractory to treatment present to our centre; however, previous studies reported that 40% of patients were nonresponders to treatment after a follow-up period of a median of 46.5 months [9].

In line with the findings of previous trials [1, 10–12,], our study stands out the negative effects of active smoking and radioiodine-induced hypothyroidism on the response to treatment in TED patients. Similarly, the correlation between the duration of hyperthyroidism and that of orbitopathy is

consistent with the results reported in the literature [1, 11]. This study also revealed the negative influence of AHT, a finding that has not been previously described; however, other authors have reported a worse response to treatment in patients with other vascular risk factors, such as high cholesterol levels [13] or diabetes mellitus [1].

Our study highlights the remarkable role of long-duration treatment approaches used herein in moderate-to severe cases (namely, intravenous corticosteroids combined with radiotherapy, and tocilizumab). These treatments were associated with a favourable outcome in the multivariable analysis (odds ratio of 7.57 ($p = 0.007$)) and with a shorter duration of active orbitopathy ($p = 0.04$).

Categorization of treatments into LDTs and the rest (non-LDTs) was performed according to the following criteria: treatments supplied for more than 3 months or with a presumed duration of action of more than 3 months were considered LDTs, whereas the rest were not. In our hands, oral corticosteroids were not used for more than 12 weeks, and intravenous corticosteroids were not used for more than one course; therefore, they were considered non-LDTs. In contrast, radiotherapy combined with intravenous corticosteroids, for which several authors have reported longer clinical effects [1, 6, 14], and tocilizumab, which can be managed and extended individually (usually for 4 to 8 months), were considered LDTs.

These findings are consistent with the current recommendations of the EUGOGO, i.e., prolong treatment with intravenous corticosteroids (12 weeks) by combining them with mycophenolate sodium for 24 weeks or adding a second course of intravenous corticosteroids if necessary. The American and the European Thyroid associations also support the use of long therapies for most clinical profiles [10]. We used radiotherapy plus intravenous corticosteroids as first-line treatment, as well as second-line treatment when other options failed. Since 2022, we have also included the latest recommendations of the EUGOGO. Therefore, we are greatly improving the results obtained with an isolated single course of intravenous corticosteroids or isolated radiotherapy.

Notice that anti-inflammatory radiotherapy is considered to be cost-effective regardless of whether it is combined with intravenous corticosteroids [15]. Thus, combined treatments as radiotherapy with corticosteroids or mycophenolate with corticosteroids can be easily administered by health care systems with fewer resources.

Notably, retrospective studies are limited by multiple confounding factors (e.g., laboratory parameters were not monitored in this study), and additional prospective studies are needed to consolidate our findings.

5. Conclusions

Active smoking, a personal history of AHT, radioiodine-induced hypothyroidism, and long-term endocrine disorders are associated with a less favourable response to treatment.

Long-duration treatment can provide a more stable outcome in adult patients with moderate-to-severe active

thyroid ophthalmopathy.

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Ethics Approval

This retrospective observational study was approved by the University Hospital of Gran Canaria Doctor Negrín ethics committee. The research was conducted in accordance with the Declaration of Helsinki (1964) and consent to participate is not required due to the non-experimental (retrospective) character of the study.

Conflicts of Interest

The authors declare no conflicts of interest.

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