Rituximab for Thyroid Eye Disease

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Purpose: To assess the efficacy and safety of rituximab-mediated B-lymphocyte depletion as treatment for thyroid eye disease (TED).

Methods: Prospective, open-label, interventional clinical trial evaluating 12 patients with TED and Clinical Activity Scores (CAS) (VISA [vision, inflammation, strabismus and appearance/exposure] classification) of 4 or greater followed for 1 year after rituximab (1000 mg) treatment, administered intravenously on days 1 and 15. CAS, peripheral B-lymphocyte levels, thyroid autoantibody levels, and thyroid function tests were recorded at baseline, 4 weeks, 8 weeks, 12 weeks, 24 weeks, 36 weeks, and 52 weeks after the second infusion. The primary endpoint was a change from baseline in CAS. Thyroid-stimulating immunoglobulin and thyroid-stimulating hormone levels were also monitored over the 12-month postinfusion observation period.

Results: CAS scores demonstrated a statistically significant decrease from baseline at each of the follow-up visits. Thyroid-stimulating immunoglobulin and thyroid-stimulating hormone levels demonstrated no statistically significant change from baseline. B-cell depletion was observed within 1 month after rituximab treatment, and peripheral B-lymphocyte counts started to increase 36 weeks after the infusion. B-cell depletion was well tolerated, and there were no adverse effects of the rituximab infusions.

Conclusions: CAS scores were significantly reduced over time in this group of 12 patients and appeared to be associated with rituximab infusion. The variable natural history of TED makes it difficult to definitively assign efficacy. The results support the continued investigation of rituximab for TED in a larger placebo-controlled trial.

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The medical treatment of thyroid eye disease (TED) remains a therapeutic challenge. The ideal medical regimen should prevent progression of the disease or control acute and long-term inflammation, with a favorable safety profile.[1] Oral and/or intravenous glucocorticoid therapy provides acute control of periocular inflammation. Long-term or high-dose glucocorticoid therapy is associated with systemic side effects.[2–5] Regional external beam radiotherapy may improve extraocular motility impairment, but efficacy in improving diplopia, proptosis, eyelid fissure height, and eyelid swelling has not been established. Radiation retinopathy, although rare, is a risk of regional external orbital radiotherapy even in patients without diabetes.[6–8]

Immunobiologic therapy, targeting specific components of the immune system with genetically engineered monoclonal antibodies, may offer acute and long-term efficacy and the desired safety profile.[9–11] Rituximab is an intravenously administered chimeric mouse-human monoclonal antibody that targets the CD20 antigen on pre-B and mature B lymphocytes. Hematopoietic stem cells, pro-B cells, and normal plasma cells

TABLE 1. Patient demographics

n	12
Age, mean (range) (years)	52.1 (34–80)
Sex, n (%)	
Male	5 (41.7)
Female	7 (58.3)
Race, n (%)	
White	7 (58.3)
Hispanic	5 (41.7)
Smoking, n (%)	
Yes	4 (33.3)
No	8 (66.7)
Laterality, n (%)	
Unilateral	1 (8.33)
Bilateral	11 (91.7)

TABLE 2. Pretreatment ophthalmic evaluation

n	12
Exophthalmometer (mm), mean (range) years	20.16 (15–31)
Palpebral fissure (mm), mean (range)	11 (8–16)
Degree of diplopia, n (%)	
None	7 (58.3)
Minimal	1 (8.3)
Moderate	0 (0.0)
Severe	4 (33.3)
Symptomatic keratopathy, n (%)	
No	7 (58.3)
Yes	5 (41.7)
Visual acuity,* n = 24 eyes (%)	
20/20	14 (58.3)
20/25–20/30	7 (29.2)
20/40–20/60	2 (8.3)
CF	1 (4.2)

Frequencies are based on the worst eye.
*Visual acuities based on Snellen chart.
CF, count fingers.

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TABLE 3. Pretreatment ophthalmic evaluation*

Patient	Exophthalmometer readings (mm)	Palpebral fissure (mm)	Degree of diplopia	Symptomatic keratopathy	Visual acuity†
1	25/26	11/10	None	None	20, 20
2	30/28	11/11	Minimal	None	CF, 30
3	23/25	10/11	None	None	20, 20
4	21/31	11/16	None	None	20, 30
5	22/18	13/11	None	None	60, 40
6	24/24	13/13	None	None	20, 20
7	17/17	17/17	Severe	Yes	20, 20
8	26/26	26/26	None	Yes	30, 30
9	20/25	20/15	Severe	Yes	25, 20
10	23/26	23/26	Severe	None	25, 25
11	21/18	21/18	Severe	Yes	20, 20
12	26/26	26/26	None	Yes	20, 20

*For exophthalmometer readings, palpebral fissure, and visual acuity, the order of data presented is OD/OS (OD, OS for visual acuity).
†Visual acuity data are based on the Snellen chart (i.e., 20/20).
CF, count fingers.

do not express the CD20 antigen, and consequently, rituximab does not induce significant immunosuppression.

In the treatment of autoimmune disease, the main effect of rituximab is to temporarily deplete the reservoir of mature B cells, usually for 6 to 9 months, reducing their role in antigen presentation and subsequent specific antibody production, thus limiting inflammation.[12,13] Rituximab received Food and Drug Administration approval in 1997 for the treatment of B-cell non-Hodgkin lymphoma, relapsed or refractory, low grade or follicular, with $CD20^+$ markers. It was approved in 2006 for the treatment of rheumatoid arthritis and is being studied as a possible treatment for a number of other autoimmune diseases.[14,15]

In the treatment of TED, efficacy has been reported in case reports and limited case series.[16–21] B cell depletion in the thyroid gland of a patient with Graves disease treated with rituximab[22] and a study of the decline in production of specific thyroid stimulating autoantibodies has been reported.[23] We report the results of a phase I/II safety and efficacy trial of 12 patients treated with rituximab for TED and their 1-year posttreatment clinical course.

METHODS

Twelve patients with active TED as defined by a Clinical Activity Score (CAS) of 4 or greater were recruited for this 2-center study. Demographic data were collected, including gender, age, laterality (i.e., affected 1 or 2 eyes), ethnicity, and smoking status at the time of presentation (Table 1). Patients underwent pretreatment ophthalmic and systemic evaluation (Tables 2 and 3). Rituximab was administered at a dose of 1000 mg, intravenously on days 1 and 15. The medication was administered in an infusion center with monitoring by a hematol-

TABLE 4. Duration of hyperthyroidism and treatment regimen

Patient	Duration of hyperthyroidism	Treatment for hyperthyroidism	Progression of ophthalmopathy after radioiodine treatment	Presence of pretibial myxedema	Previous treatment with glucocorticoids
1	3 years	RAI	Onset with hyperthyroidism, no progression after RAI	None	Oral prednisone (10–40 mg/day) over 1 year prior to enrollment
2	4 years	RAI	Onset 1 year after RAI	None	No
3	2 years	RAI	Onset with hyperthyroidism, progression 2 years after RAI	None	No
4	Subclinical	None	N/A	None	Oral prednisone (10–60 mg/day) 3 months prior to enrollment
5	1 year	Methimazole	N/A	None	No
6	9 months	Propylthiouracil	N/A	None	Oral prednisone (10–80 mg/day) tapered to 10 mg/day 1 month prior to enrollment and maintained through study
7	1 year	Tapazole, thyroidectomy	N/A	None	Two months with taper prior to referral
8	8 months	Methimazole	N/A	None	No
9	1 months	Tapazole, methimazole	N/A	None	Oral prednisone (40 mg/day) with taper to 10 mg/day for 4 months after rituximab
10	Euthyroid	None	N/A	None	Oral prednisone (40 mg/day) 1 month with taper prior to rituximab
11	9 months	Cytomel	N/A	None	Orbital radiation and prednisone 9 months prior
12	11 months	Methimazole, thyroidectomy	N/A	None	Oral prednisone four 5 day courses of 20 mg/day

TABLE 5. Efficacy (CAS and TAOS)

Week	CAS* (mean and median score)				TAOS† (mean and median score)			
	N	Mean	Median	SD	N	Mean	Median	SD
0 (baseline)	12	5.5	5.3	1.2	12	10.4	9.0	5.7
4	11	−2.6	−2.5	1.7	11	−3.7	−3.0	3.0
8	12	−2.3	−2.5	1.9	11	−3.3	−3.0	2.9
16	10	−3.6	−3.0	1.5	10	−3.3	−3.0	1.5
24	11	−3.9	−4.0	1.3	11	−4.6	−4.0	4.7
36	10	−4.2	−4.0	1.4	10	−5.9	−4.8	2.6
52	11	−4.7	−4.5	1.4	11	−8.0	−6.5	4.6

*Significant changes in change from baseline at weeks 4, 8, 16, and 36 ($p < 0.01$) and weeks 24 and 52 ($p < 0.001$).

†Significant change in change from baseline at weeks 4, 8, 16, and 36 ($p < 0.01$), week 24 ($p < 0.05$), and week 52 ($p < 0.001$).

ogist/oncologist. Standard premedication consisted of acetaminophen (1 g) and diphenhydramine (50 mg) administered orally.

Each patient demonstrated active ophthalmopathy, including persistent, debilitating, or progressive ophthalmopathy. Patients were offered rituximab as an alternative to long-term glucocorticoid use, radiation therapy, or surgery. Four patients did not receive glucocorticoids at any point in the course of their disease. Six patients were treated with glucocorticoids but underwent taper with discontinuation of the glucocorticoids at least 1 month prior to treatment. Two patients required 10 mg of prednisone maintenance therapy for 4 to 12 months after the rituximab infusions (Table 4).

The severity of disease activity or thyroid-associated ophthalmopathy as measured by the CAS and the Thyroid Associated Ophthalmopathy Scale (TAOS) were evaluated at 0 (pretreatment), 4, 8, 16, 24, 36, and 52 weeks after the second rituximab administration. Visual acuity, slit lamp, fundus examination, and Hertel testing were performed on the same schedule. The CAS, described by Mourits[24] and modified by Dolman and Rootman (VISA classification),[25] was used to quantify the effect of the treatment. The CAS used a scale of 0 to 8, based on 5 items (orbital pain, chemosis, edema, conjunctival, and eyelid injection). The TAOS scoring was used to quantify the effect of the treatment as well. This scoring system assesses orbital pain, chemosis, eyelid edema, conjunctival injection, and eyelid injection on a scale of 0 to 2, and total scores from these 5 items range from 0 to 10.

Pretreatment ophthalmic examination included visual acuity via Snellen testing, exophthalmometry readings, determination of eyelid retraction via palpebral fissure assessment, and degree of diplopia and symptomatic keratopathy. Hematologic and serologic data were collected at week 0 (pretreatment baseline), 4, 8, 16, 24, 36, and 52 weeks after the second infusion. Hematologic data included the initial level of circulating CD20-positive B lymphocytes and the postinfusion level of

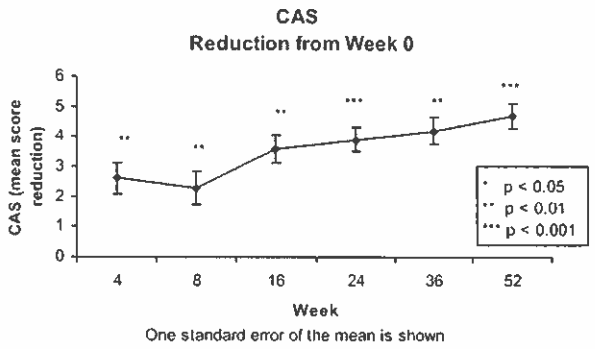

FIG. 1. Clinical Activity Score—reduction from week 0.

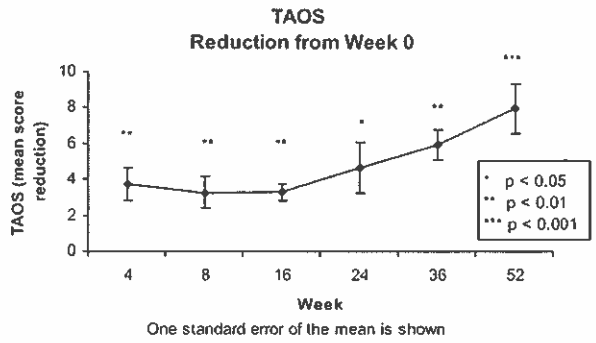

FIG. 2. Thyroid Associated Ophthalmopathy Scale—reduction from week 0.

CD19-positive B lymphocytes. Thyroid function levels including thyroid-stimulating hormone (TSH, 0.40–4.50 mIU/L) and thyroid-stimulating immunoglobulin (TSI, <125%) levels were monitored.

Adverse and serious adverse events during the study period that were reasonably or probably related to rituximab were documented throughout the study period.

Inclusion criteria included age 18 years or greater and relevant orbitopathy (CAS ≥4), with elevated serum autoantibody levels, including TSI (>125), thyrotropin receptor antibody, or antithyroid peroxidase antibodies. Patients were required to exhibit active ophthalmopathy not reversible with short-term glucocorticoid administration and were offered rituximab as an alternative to long-term glucocorticoid use, radiation therapy, or surgery. Patients were tested and required a negative serology for hepatitis B, hepatitis C, and HIV. Patients were recruited from the ophthalmic practices of the authors.

Exclusion criteria included hematologic abnormalities (neutropenia, thrombocytopenia, anemia), a history of malignancy, psychiatric disorder, cardiac or pulmonary disease, pregnancy, or active lactation.

The study was approved by the Coast Institutional Review Board. Informed consent was obtained from each patient prior to enrollment in the study. The research protocol adhered to the tenets of the Declaration of Helsinki, and the handling of data complied with Health Insurance Portability and Accountability Act requirements. The study was registered as Clinicaltrials.gov number NCT00424151.

Statistical Methods. Demographic data were summarized by descriptive statistics. Age was summarized by N, mean, and range. Gender, race, and laterality were summarized by frequency tables. For CAS and TAOS variables, data from the left and right eye were averaged for analysis. If only one eye was affected, then the affected

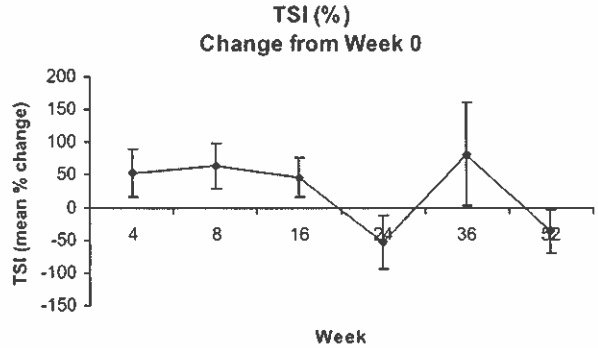

FIG. 3. Thyroid-stimulating immunoglobulin—change from week 0.

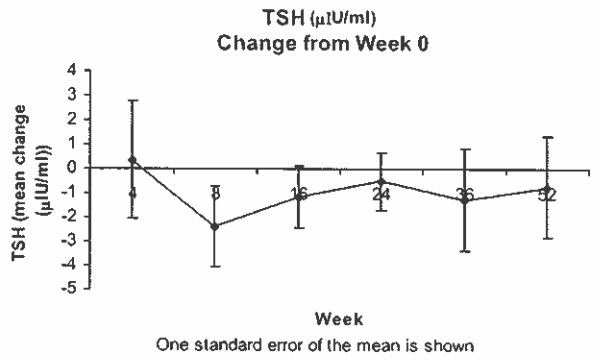

FIG. 4. Thyroid-stimulating hormone—change from week 0.

eye's data only was included in the analysis. Data were summarized by descriptive statistical methods. Comparisons of each follow-up visit with baseline were analyzed by the Wilcoxon signed-rank test.[26] TSI and TSH data were analyzed by the same statistical methods as the efficacy variables. A two-sided p value ≤ 0.05 is considered statistically significant.

Statistical computations were performed by Statistical Analysis System for Windows, Version 9.1.3.[27] Graphics displays were generated by Excel for Microsoft Office, Version 2003.[28]

RESULTS

There were 5 male and 7 female patients recruited. Ages ranged from 34 to 80 years. Seven patients were white, and 5 were of Hispanic ethnicity. The majority of patients demonstrated bilateral disease. One third of the patients were smokers at the time of recruitment. Eleven patients completed the study. One patient was not compliant with all the required follow-up visits or serologies. Phone contact revealed that she did tolerate the infusions well. This patient, as with the remaining 11 study patients, did not experience any adverse drug effects.

Of the 12 patients, 7 reported having hyperthyroidism for 1 year or less, 2 patients were hyperthyroid for 2 to 3 years, and 1 patient was hyperthyroid for 4 years. One patient was subclinical, and 1 patient was euthyroid.

Seven patients were treated with oral thyroid suppression therapy (propylthiouracil, methimazole, cytomel). Of these, 2 required subsequent thyroidectomy. Three patients were treated with radioactive iodine. Two patients did not require treatment for hyperthyroidism. None of the 12 patients demonstrated pretibial myxedema.

The mean Hertel reading was 20.16 mm, with a range of 15 to 31 mm. The mean palpebral fissure measured 11 mm, with a range of 8 to 16 mm. A total of 58.3% of patients had no diplopia, and 33.3% of patients demonstrated severe diplopia. A total of 41.7% of patients demonstrated significant keratopathy (Table 2).

The mean baseline CAS score was 5.5, with a median baseline score of 5.3. There were statistically significant decreases from baseline for weeks 4, 8, 16, 24, 36, and 52 ($p < 0.01$). The mean decreases ranged from −2.3 to −4.7. The median decreases ranged from −2.5 to −4.5 (Table 5, Fig. 1).

The mean baseline TAOS score was 10.4, with a median baseline score of 9.0. There were statistically significant decreases from baseline for weeks 4, 8, 16, 24, 36, and 52 ($p < 0.05$). The mean decreases ranged from −3.3 to −8.0. The median decreases ranged from −3.0 to −6.5 (Fig. 2).

The mean baseline TSI score was 251.3 (%), with a median baseline score of 214.0 (%). There were no statistically significant changes from baseline at any of the follow-up visits (Fig. 3).

The mean baseline TSH score was 3.45 μIU/ml, with a median baseline score of 1.11 μIU/ml. There were no statistically significant changes from baseline at any of the follow-up visits ($p > 0.05$) (Fig. 4).

CD19 levels started to increase 36 weeks postinfusion (Table 6).

TABLE 6. CD20/CD19 levels (% of gated cell population)

Patients	Baseline CD20	4 weeks CD19	8 weeks CD19	16 weeks CD19	24 weeks CD19	36 weeks CD19	52 weeks CD19
1	6	1	1	1	N/A	1	N/A
2	34	0	0	0	3	6	20
3	20	1	1	1	1	1	1
4	20	0	0	N/A	N/A	15	24
5	5	N/A	0	0	0	N/A	N/A
6	15	0	N/A	N/A	0	0	1
7	11	0	0	1	1	4	7
8	3	N/A	N/A	N/A	N/A	N/A	7
9	11	1	1	0	0	N/A	15
10	3	0	0	0	0	0	2
11	13	0	0	0	0	10	19
12	14	1	0	0	1	1	3

N/A, not available.

DISCUSSION

Twelve patients with active TED were treated with 2 courses of rituximab over a 2-week period. There were no adverse effects of the rituximab infusions and no reported side effects during the 1-year postinfusion observation period. Improvement in CASs was observed at 1 month after infusion and sustained through the 12-month observation period. Correlation between the rituximab infusion and a decline in TSI levels was not observed.

For the thyroidopathy of Graves disease and autoimmune thyroiditis, Hasselbalch first suggested the potential role of B-cell depletion with rituximab in 2003.[31] For TED, efficacy of rituximab has been reported[30,18] in several case reports and small case series.[16–20] The mechanism of action of rituximab, a CD20 antibody, in the treatment of TED seems to relate to B-cell depletion and their removal from the inflammatory process. The CD20 antigen is a 33 to 37 kD membrane-associated phosphoprotein expressed on the pre-B cells and mature B cells. B cells are precursors to plasma cells and have independent importance in presenting antigens and synthesizing cytokines such as interleukin-6, lymphotoxin, tumor necrosis factor-α, and IL-10.

The variable natural history of TED makes it difficult to assign efficacy to treatment. The observed improvement in CASs seemed to correlate with the onset of B-cell depletion. We did not observe relapse of active TED for 1 year posttreatment even with sustained elevated TSI levels and the return of B-cell levels in the peripheral blood. The results support the continued investigation of rituximab for TED with larger study populations and placebo control groups.

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CONSENSUS STATEMENT

Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO

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Introduction

Graves' orbitopathy (GO) constitutes a major clinical and therapeutic challenge (1, 2). GO is an autoimmune disorder representing the commonest and most important extrathyroidal manifestation of Graves' disease, but it may occur in patients without current or prior hyperthyroidism (euthyroid or ophthalmic Graves' disease) or in patients who are hypothyroid due to chronic autoimmune (Hashimoto's) thyroiditis (3, 4). Although the pathogenesis of GO (5–9) is beyond the scope of this document, attention is drawn to the link between the orbit and thyroid, which has important clinical and therapeutic implications. Optimal management of GO requires a coordinated approach addressing the thyroid dysfunction and the orbitopathy (10, 11).

GO is often mild and self-limiting, and probably declining in frequency, with only 3–5% of cases posing a threat to eyesight (3, 4). The onset and progression of GO are influenced by factors that are potentially controllable such as cigarette smoking, thyroid dysfunction, and choice of treatment modalities for hyperthyroidism (12, 13).

Suboptimal management of patients with GO appears to be widespread (2). The objective of this document is to provide practical information for managing patients with GO, for both non-specialists and those with special interest and expertise in this condition, and thus improve the outcomes of patients with GO. It is hoped that the document will also be useful to specialist nurses, orthoptists, and those involved in managerial roles, and that it will provide a focus for audit and research. Randomized clinical trials (RCTs) are infrequent in this field. The document should therefore be considered as a consensus statement rather than a guideline.

Methods

European Group on GO (EUGOGO) represents a multidisciplinary consortium of clinicians from the European centers, who share a commitment to improving the management of patients with GO (www.eugogo.org). A working group was formed and met in November 2006. Subsequent discussions took place electronically and at a further meeting in May 2007. After revision, the document was posted on the European Thyroid Association (ETA) and the European Society of Ophthalmic Reconstructive and Plastic Surgeons websites for wider consultation. The document was presented at the ETA Annual Meeting in Leipzig, Germany, in September 2007. Relevant articles were identified by searching MEDLINE using the terms Graves' ophthalmopathy or orbitopathy, thyroid-associated ophthalmopathy or orbitopathy, and thyroid eye disease. The definition of the Types of Evidence and the Grading of Recommendations used follows that of the Agency for Health Care Policy and Research, now Agency for Healthcare Research and Quality (www.ahrq.gov), as set out in Table 1.

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Table 1 Types of evidence and the grading of recommendations.

Level	Type of evidence
Type of evidence (based on Agency for Health Care Policy and Research (AHCPR 1992)	
Ia	Evidence obtained from the meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case–control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grade	Evidence levels	Description
Grading of recommendations (based on Agency for Healthcare Research and Quality (AHRQ 1994))		
A	Ia, Ib	Requires at least one randomized controlled trial as a part of the body of literature of overall good quality and consistency addressing the specific recommendation
B	IIa, IIb, III	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C	IV	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates the absence of directly applicable studies of good quality

√ Good practice point recommended by consensus development group.

Recommendations

Referral to combined thyroid eye clinics and initial assessment

a. Should all patients with GO be referred to combined thyroid eye clinics (10)? (Box 1)
   - All patients with GO, except for the mildest cases, should either be managed by a physician with particular expertise in managing GO or better be referred to a combined thyroid eye clinics for further assessment and management.
   - Many patients with GO never reach combined thyroid eye clinics or are referred too late to benefit from treatments (2). This practice is undesirable and may result in a suboptimal outcome and sometimes loss of vision.
   - A simple tool for assessing patients by generalist is recommended (1) and is summarized in Box 1.

Management issues of GO that should be addressed by both non-specialists and specialists

Smoking and GO

a. Is smoking related to the occurrence, severity, and progression of GO? (Box 2)
   - There is a strong and consistent association between smoking and GO (12–24).
   - Smokers suffer more severe GO (14, 15, 17) than non-smokers.
   - A dose–response relationship between the numbers of cigarettes smoked per day and the probability of developing GO has been demonstrated (21).
   - Smoking increases the likelihood of progression of GO after radioiodine therapy for hyperthyroidism (25–27).
   - Some evidence suggests that smoking either delays or worsens the outcomes of treatments for GO (28, 29).
   - There is some retrospective evidence that quitting smoking is associated with a better outcome of GO (19, 21).

Management of hyperthyroidism in patients with GO

a. Is correction of thyroid dysfunction important for GO? (Box 3)
   - Patients with uncontrolled thyroid function (both hyper- and hypothyroidism) are more likely to have severe GO than patients with euthyroidism (30–32).

b. Is there a relationship between the modality of treatment for hyperthyroidism and the course of GO?
   - Antithyroid drug (ATD) therapy (27, 30, 33) and thyroidectomy do not affect the course of GO (26, 34–36), although the role of the latter requires further investigation.
   - No particular ATD or regimen, nor any type of thyroidectomy (subtotal or total) has been demonstrated to have any advantages in terms of outcome of GO.
   - The few available RCTs on the effects of radioiodine therapy on GO show that a definite proportion of patients (~15%) develop new eye disease or experience the progression of pre-existing GO within 6 months after radioiodine therapy (25–27). In ~5% of patients, worsening persisted at 1 year and required additional treatment (25). This risk is almost eliminated by giving a short course (~3 months) of oral glucocorticoids (GCs) after radioiodine therapy (25, 27), and avoiding post-treatment hypothyroidism (32). Shorter administration of oral GCs (1–2 months) may be equally protective.

Box 1 Tools for referral of patients with GO to combined thyroid eye clinics

Primary-care physicians, general practitioners, general internists, and specialists, who have no particular expertise in managing GO, should refer patients with GO, except for the mildest cases, to combined thyroid eye clinics for further assessment and management (IV, C).

Assessments and criteria for referral recommended by EUGOGO (IV, C).
– Patients with a history of Graves' disease, who have neither symptoms nor signs of GO, require no further ophthalmological assessments and need not be referred to a combined thyroid eye clinic.
– Patients with unusual presentations (unilateral GO or euthyroid GO) should be referred, however mild their symptoms or signs, in order to make an accurate diagnosis.
– All other cases should be screened according to the protocol below (IV, C), as recommended previously by Wiersinga et al.(1)

Refer urgently if any of the following are present:
Symptoms
Unexplained deterioration in vision
Awareness of change in intensity or quality of color vision in one or both eyes
History of eye(s) suddenly 'popping out' (globe subluxation)

Signs
Obvious corneal opacity
Cornea still visible when the eyelids are closed
Disk swelling

Refer non-urgently if any of the following are present:
Symptoms
Eyes abnormally sensitive to light: troublesome or deteriorating over the past 1–2 months
Eyes excessively gritty and not improving after 1 week of topical lubricants
Pain in or behind the eyes: troublesome or deteriorating over the past 1–2 months
Progressive change in appearance of the eyes and/or eyelids over the past 1–2 months
Appearance of the eyes has changed causing concern to the patient
Seeing two separate images when there should only be one

Signs
Troublesome eyelid retraction
Abnormal swelling or redness of eyelid(s) or conjunctiva
Restriction of eye movements or manifest strabismus
Tilting of the head to avoid double vision

The reader is referred to Table 1 for an explanation of the recommendations grading system.

- The risk of exacerbation of pre-existing GO following radioiodine therapy is negligible and steroid cover can be avoided in patients with inactive eye disease, as long as post-radioiodine hypothyroidism is avoided (37, 38), and other risk factors for GO progression, including smoking (28) and high thyrotrophin receptor antibody levels (> 7.5 IU/l) (39), are absent (40).

Other simple measures that may alleviate symptoms

a. Are there worthwhile simple measures that can relieve some of the symptoms of GO? (Box 4)
   - The symptoms of corneal exposure (grittiness, watering, and photophobia) often accompany active GO, and may persist if lid retraction is severe. Such patients benefit from lubricants (3, 4).
   - Nocturnal ointment is of great benefit for incomplete eyelid closure provided the cornea is protected (3, 4). Otherwise, urgent intervention will be required.
   - Prisms may control intermittent or constant diplopia, and sleeping with head up may reduce morning eyelid swelling. Diuretics are rarely useful.
   - Botulinum toxin injection can reduce upper lid retraction (41), but this procedure should be carried out in specialist centers.

Management issues of GO, which should be addressed in specialist centers

Grading severity and activity of GO

a. What protocol should be followed for detailed assessment of patients with GO in specialist centers? (Boxes 5 and 6)
   - Making treatment decisions for patients with GO requires detailed assessment of the eyes, understanding of the natural history of the disease, insight into the impact of GO on the individual patient (42), and appreciation of the efficacy and side effects of therapies.

Box 2 Smoking and GO

All patients with Graves' disease should be informed of the risks of smoking for GO (IV, C) emphasizing the detrimental effects of smoking on:

–Development of GO (IIb, B),
–Deterioration of pre-existing GO (IIb, B),
–Effectiveness of treatments for GO (IIb, B),
–Progression of GO after radioiodine treatment (Ib, A).

If advice alone is ineffective, referral to smoking cessation clinics, or other smoking cessation strategies should be considered (IV, C).

Box 3 Management of hyperthyroidism and GO

Euthyroidism should be restored promptly and maintained stably in all patients with GO (III, B).

Frequent monitoring of thyroid status (every 4–6 weeks) is imperative in the initial phases of treatment when changes in thyroid status are expected (IV, C).

Patients with active GO given radioiodine should be offered prophylactic steroid cover (commencing with 0.3–0.5 mg of prednisone/kg bw per day orally 1–3 days after radioiodine and tapering the dose until withdrawal ~3 months later) (Ib, A). Shorter periods of glucocorticoid therapy (1–2 months) may be equally protective (IV, C).

Patients with inactive GO can safely receive radioiodine without steroid cover, as long as hypothyroidism is avoided (IIb, B), particularly if other risk factors for GO progression, such as smoking, are absent (IV, C).

Box 4 Simple measures that may alleviate symptoms in GO

Lubricant eye drops during the day and/or lubricant ointments at night-time are recommended for all patients with GO, who have symptoms of corneal exposure (III, B).

Patients with symptomatic diplopia should be given prisms if appropriate (IV, C).

Botulinum toxin injection may be considered for upper lid retraction in centers that have experience and expertise in this technique (IV, C).

b. Is it helpful to grade the severity of GO?
   - Grading the severity of GO is fraught with difficulties; however, classifying patients into broad categories facilitates decision making (Fig. 1).
   - Careful assessment of the impact of GO on quality of life (QoL) by disease-specific questionnaire (GO-QoL) (42) is fundamental in deciding whether treatments used for moderate-to-severe GO (see below) are justified in patients with mild GO.

c. Is it helpful to grade the activity of GO?
   - Grading the activity of GO is also fraught with difficulties; however, classifying patients into active/inactive GO categories is frequently possible and greatly facilitates decision making (Fig. 1). The patients with a clinical activity score (CAS) $\geq 3/7$ should be considered as having active GO (43, 44).

Management of sight-threatening GO

a. How can patients with sight-threatening GO be identified? (Boxes 7 and 8)
   - Sight-threatening GO usually occurs in the context of dysthyroid optic neuropathy (DON).
   - The risk of corneal breakdown and perforation is significant when lagophthalmos is associated with poor Bell's phenomenon (45).
   - Sight can also be threatened in patients with GO in the following rare circumstances: eyeball subluxation, severe forms of frozen globe in the presence of lagophthalmos, choroidal folds, and postural visual obscuration (46).
   - The above clinical entities require recognition and prompt medical attention (1). Box 1 can be used to identify patients with sight-threatening GO.

b. What is the treatment of choice for DON?
   - DON can be treated by systemic GCs, surgery, or both.
   - Orbital radiotherapy is not recommended in the case of DON unless as an adjunct to proved therapies.
   - High-dose i.v. GCs administered in pulses are more efficacious and associated with fewer adverse

Box 5 Activity and severity assessments in GO

EUGOGO recommends the following assessments for patients with GO in specialist centers (IV, C), as reported previously by Wiersinga *et al.* (1):

(a) Activity measures based on the classical features of inflammation: clinical activity score (CAS) is the sum of all items present (43, 44)

Spontaneous retrobulbar pain
Pain on attempted up or down gaze
Redness of the eyelids
Redness of the conjunctiva
Swelling of the eyelids
Inflammation of the caruncle and/or plica
Conjunctival edema
A CAS ≥3/7 indicates active GO

(b) Severity measures

Lid aperture (distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed, and with distant fixation)
Swelling of the eyelids (absent/equivocal, moderate, severe; www.eugogo.org)
Redness of the eyelids (absent/present; www.eugogo.org)
Redness of the conjunctivae (absent/present; www.eugogo.org)
Conjunctival edema (absent, present; www.eugogo.org)
Inflammation of the caruncle or plica (absent, present; www.eugogo.org)
Exophthalmos (measured in millimeter using the same Hertel exophthalmometer and same intercanthal distance for an individual patient)
Subjective diplopia score (0=no diplopia; 1=intermittent, i.e. diplopia in primary position of gaze, when tired or when first awakening; 2=inconstant, i.e. diplopia at extremes of gaze; 3=constant, i.e. continuous diplopia in primary or reading position)
Eye muscle involvement (ductions in degrees; www.eugogo.org)
Corneal involvement (absent/punctate keratopathy/ulcer)
Optic nerve involvement (best-corrected visual acuity, color vision, optic disk, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected

Box 6 Severity classifications in GO

EUGOGO recommends the following classification of patients with GO (IV, C):

1. ***Sight-threatening GO: Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown. This category warrants immediate intervention.***
2. ***Moderate-to-severe GO: Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients with moderate-to-severe GO usually have any one or more of the following: lid retraction ≥2 mm, moderate or severe soft tissue involvement, exophthalmos ≥3 mm above normal for race and gender, inconstant, or constant diplopia.***
3. ***Mild GO*: patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have only one or more of the following: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos <3 mm above normal for race and gender, transient or no diplopia, and corneal exposure responsive to lubricants.**

effects than oral or retrobulbar steroids (3, 4, 47–51) (Table 2).

- Improvement of optic nerve function can be expected after high-dose i.v. GCs within 1–2 weeks (52).
- Relapse of DON may occur when systemic GCs are withdrawn too quickly (see Management of moderate-to-severe GO) (3, 4).
- Decompression surgery can lead to rapid resolution of DON with an acceptable adverse effect profile. However, GCs and squint surgery are frequently required, and occasionally further decompression surgery is necessary (53). Immediate decompression surgery as first-choice therapy does not appear to result in a better outcome compared with i.v. GCs as first choice, nor does it obviate the need for subsequent GC therapy (54).

c. What is the treatment of choice for sight-threatening corneal breakdown?

- In severe, sight-threatening corneal breakdown when the cornea cannot be protected by the closed eyelid, hourly topical lubricants are indicated; however, this intervention alone may be insufficient to prevent ulceration, thinning, and perforation. In such cases, specific measures to improve eyelid closure are required.
- A moisture chamber or temporary eye closure by blepharorrhaphy, tarsorrhaphy, or botulinum

toxin injections can help temporize until corneal healing occurs (55).
- The effect of GCs on severe corneal exposure has never been specifically addressed.
- Most of the studies on the effects of orbital decompression report a reduction in symptoms associated with exposure keratopathy; rarely severe corneal ulcers may be refractory to decompression surgery if lagophthalmos persists (56).

Management of moderate-to-severe GO

a. Does every patient with moderate-to-severe GO require treatment? (Boxes 9 and 10)
   - Many patients in this category should be considered for treatment, with the exception of patients who are asymptomatic or unwilling to have treatment.
   - Patients with moderate-to-severe and active (CAS $\geq$3/7) GO should be treated with immunosuppressive treatment modalities, while those with inactive GO may benefit from rehabilitative surgery (see below; Fig. 1).

b. What are the non-surgical treatments of choice for moderate-to-severe GO?
   - *Glucocorticoids.* GC therapy has been used in the management of GO through oral, local (retrobulbar or subconjunctival), or i.v. routes (35). *Oral GC* therapy (starting dose, 80–100 mg prednisone (or ~1 mg/kg bw) or equivalent) requires high doses for prolonged periods of time. No randomized, placebo-controlled studies have been performed. Open trials or randomized studies, in which oral GCs were compared with other treatments (47, 48, 50, 57–62), show a favorable response in ~33–63% of patients, particularly for soft tissue changes, recent onset eye muscle involvement, and DON. The eye disease frequently flares up on tapering or withdrawing GCs. Side effects are frequent. Prolonged oral GC treatment is associated with a risk of osteoporosis (49), which may be decreased using bisphosphonates or other antiresorptive drugs (63, 64). *Retrobulbar or subconjuctival GC* therapy is less effective than oral GCs (65). *Intravenous GC pulse therapy* is more effective than oral GC (response rates ~80% vs ~50%; Table 2) (3, 4, 47–51, 66). Evidence for the superiority of any of the different i.v. GC schedules is lacking (Table 2). Although i.v. GCs are tolerated better than oral GCs (47, 50), acute liver damage and a risk of life-threatening liver failure has been reported in association with very high cumulative doses (67, 68) in ~0.8% of patients (68). Intravenous

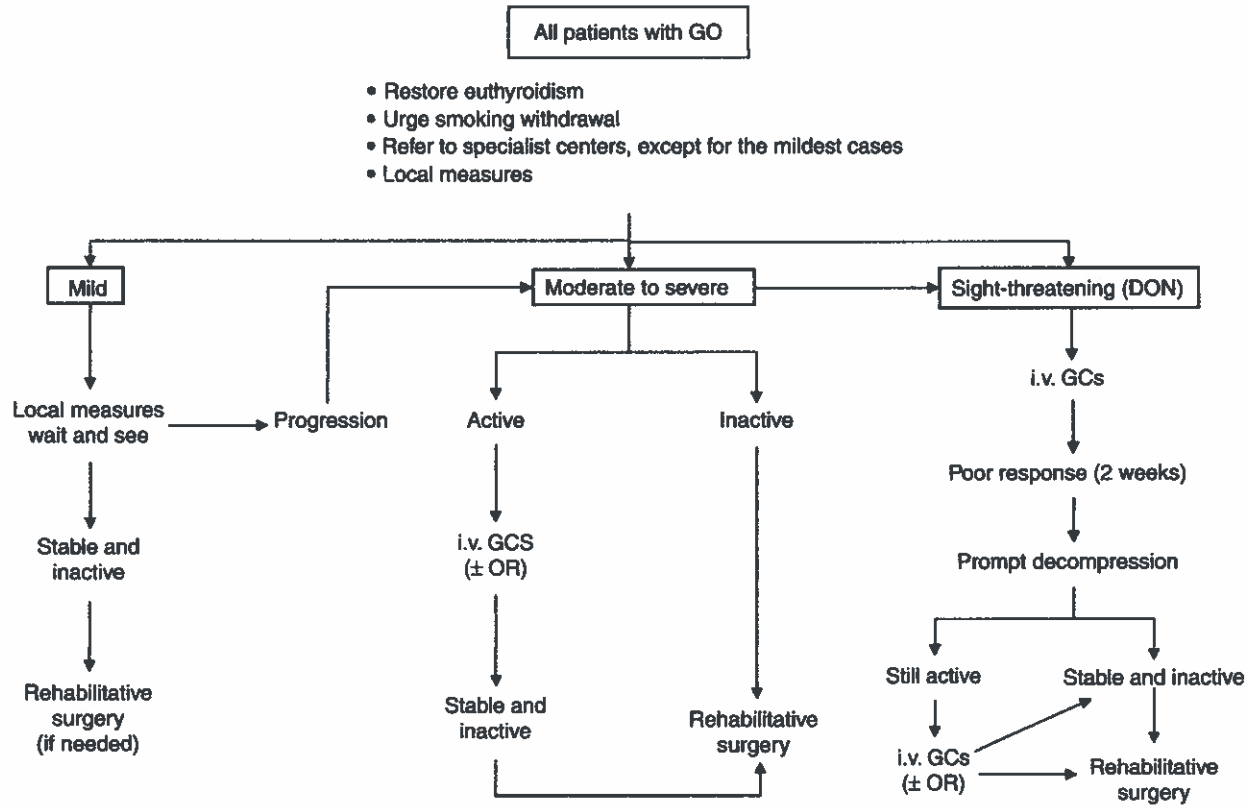

Figure 1 Management of Graves' orbitopathy. Rehabilitative surgery includes orbital decompression, squint surgery, lid lengthening, and blepharoplasty/browplasty. i.v. GCs, intravenous glucocorticoids; OR, orbital radiotherapy; DON, dysthyroid optic neuropathy. For the definitions of GO severity and activity, see text.

Box 7 Glucocorticoids and orbital decompression in DON

Glucocorticoids (GCs) and surgical decompression of the orbit are the only treatments proved to be effective in patients with DON (III, B).

High-dose i.v. GCs is the preferred first-line treatment for DON (III, B).

If the response to i.v. GCs is absent or poor after 1–2 weeks, or the dose/duration of steroid required induces significant side effects, prompt orbital decompression should be carried out (IV, C).

Orbital decompression should be offered promptly to patients with DON or corneal breakdown who cannot tolerate GCs (III, B).

Both i.v. GC therapy and orbital decompression surgery should only be undertaken in centers with appropriate expertise (IV, C).

GCs are safe if the cumulative dose is <8 g methylprednisolone in one course of therapy (69). Bisphosphonates should be considered for patients receiving i.v. GCs, although no RCTs have specifically addressed this issue.

- *Orbital radiotherapy.* The reported response rate to orbital radiotherapy (OR) in open trials is ~60% (3, 4, 66). A cumulative dose of 20 Gy per orbit fractionated in ten doses over a 2-week period is commonly used (70), but an alternative regimen of 1 Gy per week over a 20-week period was equally effective and better tolerated (71). Higher doses are no more effective (72). A lower cumulative dose of 10 Gy was found to be as effective as the standard 20 Gy regimen (71). The response to OR did not differ from oral prednisone in an RCT (60). Two recent RCTs have shown that OR is more effective than sham irradiation in improving diplopia and eye muscle motility (73, 74). Another RCT has questioned the efficacy of OR (75). OR is usually well tolerated, but may cause transient exacerbation of ocular symptoms, which is preventable with concomitant GC administration (3, 66). Data on long-term safety are reassuring (76–78), but theoretical concerns about carcinogenesis remain for younger patients, particularly those under the age of 35 years (70, 76–78). Although cataracts can occur earlier after OR than naturally, they are easily treated by surgery. Retinal microvascular abnormalities have been detected in a minority of patients (79), mostly in those with concomitant severe hypertension or diabetic retinopathy, and these two comorbidities are considered absolute contraindications to OR (80, 81). It is possible that diabetes, even in the absence of retinopathy, represents a risk factor for the development of retinal changes after OR (78), but the evidence is less clear (77). Thus, diabetes without retinopathy may be regarded as a relative contraindication to OR (see also Box 12).
- *Combination of GC* (either orally or locally) *with OR* is more effective than either treatment alone (57, 82). It is unclear whether i.v. GCs with OR are more efficacious than i.v. GCs alone.
- *Treatments of marginal or unproven value* include *somatostatin analogs* (83–86), *azathioprine* (87), *ciamexone* (88), and *i.v. immunoglobulins* (62, 89). Two studies have shown the superiority of the combination of oral GCs and *cyclosporine* than either treatment alone (58, 59). The potential usefulness of immunomodulatory agents, such as rituximab (90) or etanercept (91), has been suggested by open studies, but no RCTs have been carried out as yet.

Box 8 Sight-threatening corneal breakdown in GO

Sight-threatening corneal breakdown should be managed as an emergency (IV, C).

The management of sight-threatening corneal breakdown includes:
Frequent topical lubricants (preservative-free topical lubricants for hyperallergic patients), moisture chambers, blepharorrhaphy, tarsorrhaphy, or other temporary measures until the cornea has healed (IV, C).

Consideration of systemic GCs or surgical decompression when the above measures alone are ineffective (IV, C).

In the event of corneal perforation/severe ulceration, appropriate antibiotics, and emergency glueing, amnion membrane as shield, or corneal grafting need to be considered (IV, C).

Once the corneal breakdown is brought under control, it is imperative that treatment is offered to improve lid closure and thus prevent further episodes of corneal breakdown (IV, C).

Table 2 Randomized clinical trials of i.v. methylprednisolone versus oral prednisone.

Treatment randomization		Response rate (%)			
Group A	Group B	Group A (%)	Group B (%)	*P* value	Reference
i.v. methylprednisolone[a] +radiotherapy[b] (n=41)	Oral prednisone[c]+ radiotherapy[b] (n=41)	88	63	<0.02	Marcocci *et al.* (47)
i.v. methylprednisolone[d] (n=35)	Oral prednisone[e] (n=35)	77	51	<0.01	Kahaly *et al.* (50)

[a]15 mg/kg^{-1} for four cycles, then 7.5 mg/kg^{-1} for four cycles; each cycle consisted of two infusions on alternate days at 2-week intervals.
[b]20 Gy in ten daily doses of 2 Gy over 2 weeks.
[c]100 mg daily for 1 week, then weekly reduction until 25 mg daily, and then tapering by 5 mg every 2 weeks.
[d]500 mg once weekly for 6 weeks, 250 mg once weekly for 6 weeks, total treatment period: 12 weeks.
[e]100 mg daily starting dose, tapering by 10 mg per week, total treatment period: 12 weeks.

c. Do non-surgical treatments reduce the subsequent need for rehabilitative surgery or do they adversely interfere with it?
   - No RCTs have been performed to investigate specifically whether non-surgical treatments reduce the subsequent need for rehabilitative surgery, so this important question remains unanswered.
   - The theoretical concern that radiation-induced fibrosis may reduce orbital compliance, and hence compromises subsequent therapies, is not supported by the available evidence (92, 93).

d. What is the role of surgery in moderate-to-severe GO?
   - Rehabilitative surgery includes one or more of the following procedures: (a) orbital decompression (the usual indications being disfiguring exophthalmos, troublesome retroocular pain/discomfort, and/or grittiness associated with minor exposure keratopathy not amenable to topical therapies (94); (b) squint correction; (c) lid lengthening; and (d) blepharoplasty/browplasty. If more than one procedure is required, the sequence should be as outlined above.
   - Orbital decompression for disfiguring exophthalmos is best deferred until the orbitopathy has been inactive for at least 6 months. However, orbital decompression can be considered also in patients with active GO who are intolerant or non-responsive to GCs, if waiting for spontaneous inactivation of GO can potentially be hazardous for visual function.
   - Almost all studies show the efficacy and relative safety of orbital decompression (46, 94–101); however, the available studies do not allow any meaningful comparison of the available techniques (93, 94, 100, 101).
   - Eye muscle and lid surgeries are effective treatments for correcting diplopia and improving lid function and appearance.
   - Rehabilitative surgery yields the best results when GO is inactive. Very long duration of GO is no contraindication to rehabilitative decompression (100).

Box 9 Treatment of moderate-to-severe GO that is ACTIVE

The treatment of choice for moderate-to-severe and active (CAS ≥3/7) GO is pulses of i.v. glucocorticoids (GCs) (Ib, A). This treatment should be undertaken in centers with appropriate expertise (IV, C).

The total cumulative dose of methylprednisolone should not exceed 8 g in one course of therapy (III, B).

Patients being treated with high-dose i.v. GC should be first screened for liver dysfunction, hypertension, history of peptic ulcer, diabetes, urine infection, and glaucoma, and then monitored for side effects (IV, C).

Bisphosphonates are recommended when long-term (>3 months) oral GC therapy (average daily dose >5 mg prednisone or equivalent) is used (Ia, A). It is reasonable to suggest the use of antiresorptive agents also when GCs are used i.v. (IV, C).

Orbital irradiation (OR) should be considered in patients with active disease who have diplopia or restricted motility (Ib, A). OR with lower cumulative doses (10 Gy) may be as effective as and better tolerated than OR with higher doses (20 Gy) (Ib, A). Doses >20 Gy are not recommended (IV, C).

Caution should be exercised before administering OR to patients younger than 35 years; OR must be avoided in patients with diabetic retinopathy or severe hypertension (III, B).

The combination of oral GCs with OR is more effective than either treatment alone (Ib, A), but randomized clinical trials indicating that the combination of i.v. GCs with OR is better than i.v. GCs alone are lacking (IV, C).

Box 10 Timing and the order of surgery for GO

The timing and the order of surgical interventions should be carefully planned (IV, C).

Surgical management should proceed in the following sequence: orbital decompression, then squint surgery, and then lid lengthening with or followed by blepharoplasty/browplasty, since side effects of the preceding step can interfere with the step that follows (III, B).

Rehabilitative surgery should only be performed in patients who have had inactive GO for at least 6 months (III, B).

Rehabilitative surgery should only be undertaken in centers with appropriate expertise (IV, C).

e. Does orbital decompression compromise subsequent non-surgical therapy?
   - In the rare event of reactivation of GO after rehabilitative surgery, systemic GCs, and/or OR can be used with the usual expected efficacy (99).

Management of mild GO

a. Are GCs and/or orbital radiotherapy indicated or useful in mild GO? (Box 11)
   - Although GCs and OR are of potential value in mild disease (60, 73, 74), they are usually not recommended as the risks outweigh the benefits. Simple measures (Box 4) are usually sufficient.

b. Is a 'wait-and-see' strategy reasonable?
   - GO is a self-limiting disease. In the absence of efficacious treatments with minimal side effects, watchful waiting is appropriate for the majority of patients with mild disease, especially those with a satisfactory QoL, as assessed by the EUGOGO questionnaire (www.eugogo.org).

c. How should mild eyelid retraction, soft tissue swelling, and exophthalmos be managed, and when in the course of the orbital disease?
   - Sometimes even mild eyelid retraction, soft tissue swelling, or exophthalmos has a profoundly negative impact on psychosocial functioning and QoL, depending on the circumstances of the individual (102, 103).
   - Treatment might be offered to these patients if careful consideration of risks and benefits favors intervention.

Special situations

a. How should a diabetic or hypertensive patient with moderate-to-severe or sight-threatening GO be treated? (Boxes 12 and 13)
   - Systemic GCs can induce or exacerbate diabetes and/or hypertension. However, the indications for steroid use in patients with diabetes and/or hypertension are no different than in other patients. Close monitoring of glycemic control and blood pressure is important. Thiazide or loop diuretics should be used with caution during high-dose GC therapy to avoid hypokalemia. The same principle applies to surgical treatments.
   - OR may increase the risk of retinopathy in diabetic and hypertensive patients (77, 78, 80, 81), at least using a 20 Gy cumulative dose.
   - Diabetes and/or hypertension are not contra-indications to surgical orbital decompression or other surgical treatments for GO.

b. What is the best therapeutic approach to GO in childhood?
   - GO is rare in childhood because of the low incidence of Graves' disease in this age group (104, 105). The eye disease is usually milder in children than in adults and often stabilizes and eventually resolves without intervention (105).
   - Achieving and maintaining euthyroidism are as important objectives as in adult patients.
   - Exposure to smoking (active and, possibly, passive) is probably as detrimental as in adults (106–108).
   - Because of the effects on growth, GCs should be avoided unless DON is present. OR is contra-indicated in children. Somatostatin analogs have

Box 11 Management of mild GO

Glucocorticoids are rarely justified in mild GO as the risks outweigh the benefits (IV, C).

Watchful waiting is appropriate for the majority of patients with mild GO (IV, C).

In a minority of patients with mild disease, quality of life may be so profoundly affected as to justify using treatments as for moderate-to-severe disease (IV, C).

Box 12 Diabetes or hypertension and GO

Diabetes and/or hypertension should not be considered as contraindications to GC or surgical treatments for GO (IV, C).

Diabetic retinopathy and/or severe hypertension are absolute contraindications for OR (III, B).

Diabetes without retinopathy is a relative contraindication for OR, but evidence is less clear (IV, C).

Box 13 GO in children

Euthyroidism should be restored promptly and maintained in children as in adults (III, B).

Children with GO should be managed conservatively if vision is not threatened (IV, C).

Simple measures to address specific symptoms can be utilized as for adults (Box 4) (IV, C).

Glucocorticoids should be avoided in children (IV, C).

Orbital radiotherapy is contraindicated in children (IV, C).

Exposure to active and, possibly, passive smoking should be avoided (IV, C).

been used in isolated cases, but RCTs on efficacy and safety are lacking (109).

- Orbital surgery may be necessary in the cases of severe exophthalmos, but for most patients a conservative and expectant approach is appropriate.

Summary of consensus

a. All patients with GO should (Fig. 1):
   Be referred to specialist centers;
   Be encouraged to quit smoking;
   Receive prompt treatment in order to restore and maintain euthyroidism.
b. Patients with sight-threatening GO should be treated with i.v. GCs as the first-line treatment; if the response is poor after 1–2 weeks, they should be submitted to urgent surgical decompression.
c. The treatment of choice for moderate-to-severe GO is i.v. GCs (with or without OR) if the orbitopathy is active; surgery (orbital decompression, squint surgery, and/or eyelid surgery in this order) should be considered if the orbitopathy is inactive.
d. In patients with mild GO, local measures and an expectant strategy are sufficient in most cases, but treatment may be justified if QoL is affected significantly.

In memoriam

This document is dedicated to the memory of Mark Prummel (1956–2005), one of the founders of EUGOGO, who greatly contributed to expanding our understanding of clinical and therapeutic aspects of GO.

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ORIGINAL ARTICLE

Selenium and the Course of Mild Graves' Orbitopathy

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ABSTRACT

BACKGROUND

Oxygen free radicals and cytokines play a pathogenic role in Graves' orbitopathy.

METHODS

We carried out a randomized, double-blind, placebo-controlled trial to determine the effect of selenium (an antioxidant agent) or pentoxifylline (an antiinflammatory agent) in 159 patients with mild Graves' orbitopathy. The patients were given sodium selenite (100 μg twice daily), pentoxifylline (600 mg twice daily), or placebo (twice daily) orally for 6 months and were then followed for 6 months after treatment was withdrawn. Primary outcomes at 6 months were evaluated by means of an overall ophthalmic assessment, conducted by an ophthalmologist who was unaware of the treatment assignments, and a Graves' orbitopathy–specific quality-of-life questionnaire, completed by the patient. Secondary outcomes were evaluated with the use of a Clinical Activity Score and a diplopia score.

RESULTS

At the 6-month evaluation, treatment with selenium, but not with pentoxifylline, was associated with an improved quality of life ($P<0.001$) and less eye involvement ($P=0.01$) and slowed the progression of Graves' orbitopathy ($P=0.01$), as compared with placebo. The Clinical Activity Score decreased in all groups, but the change was significantly greater in the selenium-treated patients. Exploratory evaluations at 12 months confirmed the results seen at 6 months. Two patients assigned to placebo and one assigned to pentoxifylline required immunosuppressive therapy for deterioration in their condition. No adverse events were evident with selenium, whereas pentoxifylline was associated with frequent gastrointestinal problems.

CONCLUSIONS

Selenium administration significantly improved quality of life, reduced ocular involvement, and slowed progression of the disease in patients with mild Graves' orbitopathy. (Funded by the University of Pisa and the Italian Ministry for Education, University and Research; EUGOGO Netherlands Trial Register number, NTR524.)

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Approximately half the patients with Graves' disease have ocular involvement (Graves' orbitopathy).[1] Moderately severe and active forms of Graves' orbitopathy can be effectively treated with glucocorticoids, orbital irradiation, or both,[1,2] whereas milder forms may improve spontaneously and generally require only local measures to control symptoms (i.e., artificial tears, ointments, and prisms).

A wait-and-see strategy in which patients are monitored until symptoms worsen can be challenged. First, many patients with even mild Graves' orbitopathy have a substantial decrease in their quality of life, as assessed either by general health–related quality-of-life questionnaires[3] or by a Graves' orbitopathy–specific quality-of-life questionnaire (GO-QOL).[4] Second, in a natural-history study of mild Graves' orbitopathy, spontaneous improvement occurred in about 20% of patients, but eye disease remained static in 65% and progressed in 15%.[5] Thus, therapy would seem justified. Treatment should be affordable, well tolerated, and widely available. Two agents that may potentially inhibit pathogenic mechanisms believed to be relevant in Graves' orbitopathy are selenium and pentoxifylline.

Selenium is a trace mineral and an essential nutrient for selenocysteine synthesis.[6] Selenocysteine is incorporated into several selenoproteins, mostly enzymes, in which selenium acts as a reduction–oxidation center and functions as an antioxidant. A number of in vitro studies have suggested that increased generation of oxygen free radicals plays a pathogenic role in Graves' orbitopathy.[7-9] Selenium also has an important effect on the immune system[6,10] and might be beneficial in patients with Hashimoto's thyroiditis[11,12] or Graves' disease.[13]

Pentoxifylline is a nonspecific phosphodiesterase inhibitor used for the treatment of intermittent claudication.[14] It also has antiinflammatory and immunomodulatory effects[15-17] and an in vitro inhibitory effect on HLA-DR expression and glycosaminoglycan secretion by orbital fibroblasts.[18,19] All these factors are relevant to the pathogenesis of Graves' orbitopathy.[20,21] One small pilot study has suggested that pentoxifylline might be beneficial in patients with Graves' orbitopathy.[22]

On behalf of the European Group on Graves' Orbitopathy (EUGOGO), we report the results of a multicenter, randomized, double-blind, placebo-controlled clinical trial that investigated whether selenium or pentoxifylline may be beneficial in patients with mild Graves' orbitopathy.

METHODS

PATIENTS AND STUDY DESIGN

From January 2005 through January 2009, all consecutive patients seen at six EUGOGO centers (in Amsterdam, Mainz [Germany], Olten [Switzerland], Pisa [Italy], Thessaloniki [Greece], and Varese [Italy]) who had mild signs or symptoms of Graves' orbitopathy of less than 18 months' duration were invited to participate in the study if they met the inclusion criteria. (For a list of inclusion and exclusion criteria, see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

The goal of the study was to determine whether selenium or pentoxifylline, as compared with placebo, could affect the course of Graves' orbitopathy (either by enhancing improvement or preventing worsening) and could improve the patients' quality of life. The study lasted 1 year and consisted of a 6-month period of intervention followed by a 6-month period of follow-up.

The two drugs and the placebo were administered orally. Selenium was given as sodium selenite in a dose of 100 μg twice daily, pentoxifylline (Trental, Sanofi Aventis) was given at a dose of 600 mg twice daily, and placebo was given twice a day. Selenium and placebo tablets were prepared by Gelfipharma to look identical to pentoxifylline. Randomization was performed centrally at the Amsterdam site, with stratification according to center in blocks of six. Two each of the six sealed envelopes containing the assignments were designated lot 1, lot 2, or lot 3. The tablets were delivered in identical boxes (designated lot 1, 2, or 3) and were given to the patients by the local endocrinologist, who was unaware of the content of the lots.

The study was approved by the institutional review boards of the participating centers and by the ethics committee of the Academic Medical Center at the University of Amsterdam. Written informed consent was obtained from all participants before enrollment. The study was conducted in compliance with the protocol, available at NEJM.org.

The study was designed by the EUGOGO group. All the authors gathered the data and vouch for its accuracy. Statistical analyses were performed by

one of the authors. The first author wrote the initial draft of the manuscript, and all authors were involved in the revision and decision to submit the manuscript for publication. All study drugs were purchased from the manufacturer.

STUDY PROCEDURES AND END POINTS

Patients were evaluated at baseline and at 3, 6, and 12 months. Eye examinations were performed by an ophthalmologist who was not aware of the treatment assignments, using a modified EUGOGO case record form. At all follow-up visits, the same ophthalmologist at each center evaluated the patients and recorded the eyelid aperture size (measured in millimeters), any soft tissue involvement (with reference to the Color Atlas at www.eugogo.eu),[23] exophthalmos (measured in millimeters with the use of the same Hertel exophthalmometer in each center), eye-muscle involvement (with the extent of ductions measured in degrees), and visual acuity (measured in decimals with the use of the Snellen chart).

The Clinical Activity Score consists of seven items: spontaneous retrobulbar pain, pain on attempted eye movements (upward, side-to-side, and downward gazes), conjunctival redness, redness of the eyelids, chemosis, swelling of the caruncle, and swelling of the eyelids; the final score is the sum of all items present.[24] The Gorman diplopia score includes four categories: no diplopia (absent), diplopia when the patient is tired or awakening (intermittent), diplopia at extremes of gaze (inconstant), and continuous diplopia in the primary or reading position (constant).[25] Quality of life was evaluated with the use of the previously validated GO-QOL questionnaire,[4,26] which is available in several languages. Blood samples were obtained at all visits to assess thyroid function (levels of serum free thyroxine, total or free triiodothyronine, and thyrotropin) and to detect autoantibodies against thyroid peroxidase and against the thyrotropin receptor. Any side effects of the treatments were recorded at all follow-up visits.

There were two primary outcome measurements: the assessment of eye changes by an ophthalmologist who was unaware of the treatment assignments, and the score on the GO-QOL questionnaire filled out by the patient. The primary end points were comparisons of outcome rates on the basis of the overall ophthalmic assessment and the GO-QOL score (improved, unchanged, or worse) (Table 1 in the Supplementary Appendix) at 6 months between the patients assigned to one of the two active treatments and those assigned to placebo. The overall ophthalmic outcome is a composite score based on multiple items; the use of a composite score circumvents the problem arising from the presence of improvement in one item and simultaneous worsening in another item. Secondary outcome measurements were the changes in the diplopia score and in the seven-item Clinical Activity Score at 6 months.

The visit at 3 months was scheduled to check thyroid status and adherence to treatment. The 12-month observation was scheduled as exploratory, for the sole purpose of determining whether the treatment effects at 6 months had been maintained.

STATISTICAL ANALYSIS

The study was designed to compare selenium and placebo and to compare pentoxifylline and placebo. The sample size was calculated on the basis of the results of a previous observational study in patients with Graves' orbitopathy that showed improvement in 20% of patients, no change in 65%, and worsening in 15% in the absence of specific treatment.[5] We tested the hypothesis that treatment with selenium or pentoxifylline would result in an increase of 25 percentage points (from 20% to 45%) in the proportion of patients with improvement after 6 months of treatment. To detect such a difference with 80% power and a significance level of 0.05, each study group was designed to comprise 52 patients.

Patients who were withdrawn from the study prematurely because of side effects, lack of adherence to the study regimen, or disease progression requiring specific treatments were included in the primary analysis provided that they were available for evaluation at the 3-month visit. Results of their last assessment were carried forward and evaluated as the last visit. Patients who were lost to follow-up before the visit at 3 months were excluded from the analysis.

Categorical variables were compared with the use of the chi-square test or Fisher's exact test. The two-sided t-test and the Mann–Whitney test were used to evaluate differences in the changes in the GO-QOL score and in the Clinical Activity Score at 6 and 12 months, as compared with baseline, between each of the active-treatment groups and the placebo group. Levels of thyroid auto-

antibodies at the end of treatment (at 6 months) were compared with baseline levels with the use of the paired-sign test for thyroid peroxidase autoantibodies (since different assay methods were used at different centers) and the Wilcoxon signed-rank test for autoantibodies against the thyrotropin receptor. The effectiveness of the treatments in preventing deterioration of Graves' orbitopathy was evaluated by comparing the number of patients whose eye disease got worse with the number of patients whose eye disease either improved or remained unchanged.

A P value of less than 0.05 was considered to indicate statistical significance. We planned to use the Benjamini–Hochberg correction for multiple comparisons for analysis of between-group differences in the primary end points.[27] P values for secondary end points and for end points at 12 months were calculated for exploratory purposes.

RESULTS

PATIENTS

From January 2005 through January 2009, a total of 204 eligible patients were invited to participate in the study (Fig. 1). Of these 204 patients, 45 declined and 159 were randomly assigned to selenium (55 patients), pentoxifylline (52), or placebo (52). The clinical characteristics of the patients who declined did not differ from those of the patients assigned to treatment. Seven patients left the study during the first month owing to withdrawal of consent (1 in the selenium group and 2 in the placebo group) or to drug-related adverse effects (4 in the pentoxifylline group), and these patients were not included in the final analysis. The remaining 152 patients (54 in the selenium group, 48 in the pentoxifylline group, and 50 in the placebo group) underwent at least the first

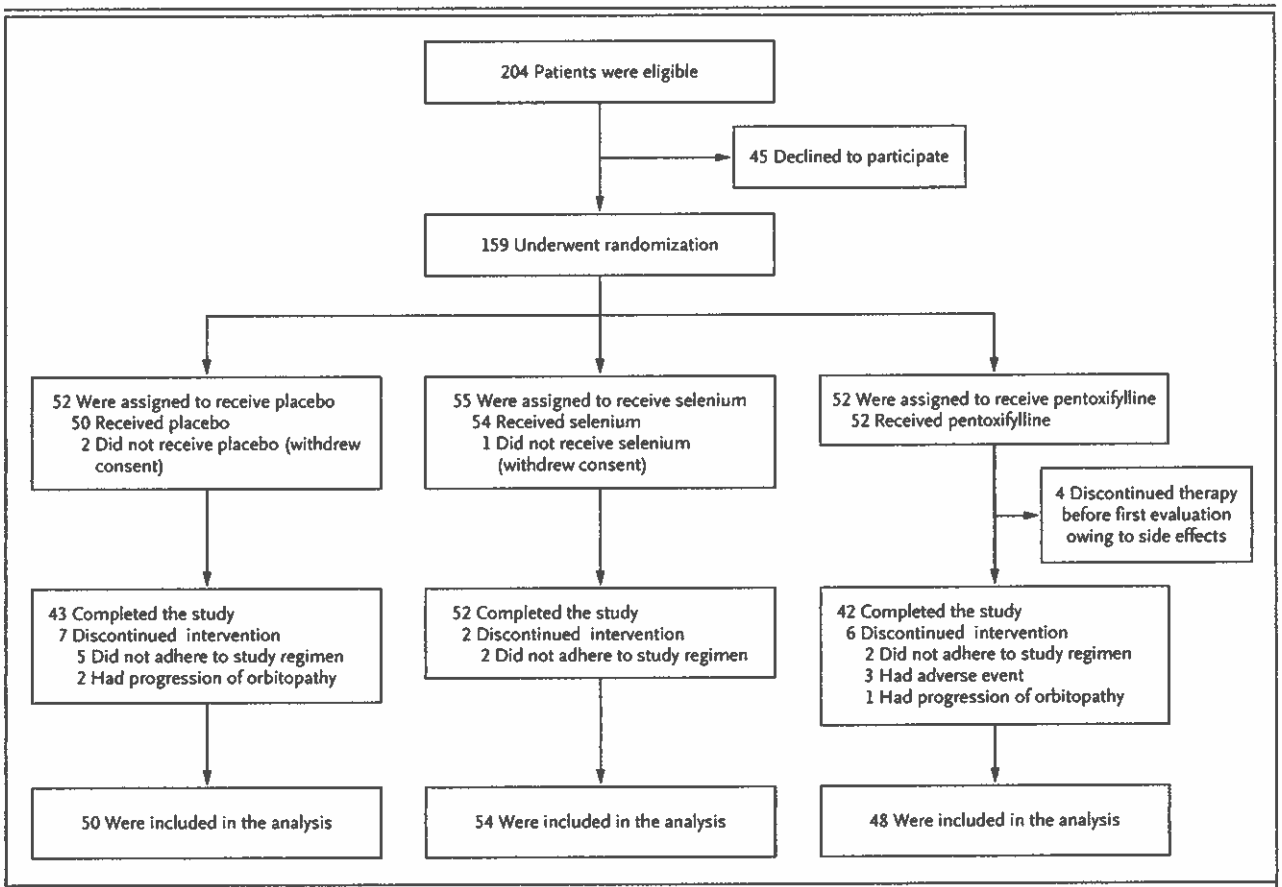

Figure 1. Enrollment, Randomization, and Follow-up of Study Patients.

Seven of the 159 patients enrolled and randomly assigned to treatment were not included in the analysis because they either withdrew consent (3 patients) or discontinued therapy before the 3-month evaluation because of drug-related adverse effects (4 patients).

evaluation at 3 months and were included in the final analysis.

The baseline characteristics of the study patients and the number recruited per center are shown in Table 1. Of the 152 participants, 137 (90%) completed the study (52 in the selenium group [96%], 42 in the pentoxifylline group [87%], and 43 in the placebo group [86%]); 15 withdrew prematurely because of lack of adherence (2, 2, and 5 patients in the three groups, respectively); side effects (0, 3, and 0 patients, respectively); or progression of Graves' orbitopathy requiring treatment with intravenous glucocorticoids, orbital radiotherapy, or both (0, 1, and 2 patients, respectively).

Thyroid-function tests confirmed euthyroidism in all patients; a few patients required minor adjustments in the dose of antithyroid drug or levothyroxine. Levels of thyroid peroxidase autoantibodies declined in both the selenium group

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Selenium (N=54)	Placebo (N=50)	Pentoxifylline (N=48)
Demographic and clinical characteristics			
Age — yr	43.0±11.0	44.6±10.7	43.7±12.4
Female sex — no. of patients (%)	48 (89)	41 (82)	37 (77)
Race — no. of patients (%)†			
White	52 (96)	50 (100)	48 (100)
Asian	1 (2)	0	0
Black	1 (2)	0	0
Thyroid disease — no. of patients (%)			
Graves' disease	51 (94)	43 (86)	46 (96)
Chronic autoimmune thyroiditis	2 (4)	3 (6)	2 (4)
Euthyroid Graves' disease	1 (2)	4 (8)	0
Previous thyroid treatment — no. of patients (%)			
Radioiodine	4 (7)	4 (8)	6 (12)
Thyroidectomy	4 (7)	9 (18)	6 (12)
Current thyroid treatment — no. of patients (%)			
Antithyroid drugs‡	41 (76)	34 (68)	35 (73)
Levothyroxine	9 (17)	9 (18)	11 (23)
None	4 (7)	7 (14)	2 (4)
Duration of eye symptoms or signs — mo	7.7±5.8	6.1±4.6	6.0±4.6
Current smoker — no. of patients (%)	23 (43)	25 (50)	17 (35)
Biochemical characteristics			
Thyrotropin — mU/liter			
Median	0.6	0.7	1.1
Interquartile range	0.3–2.1	0.3–2.0	0.5–2.2
Thyrotropin-receptor autoantibodies — IU/liter			
Median	6.8	4.3	4.4
Interquartile range	3.5–23.0	2.0–15.0	1.3–11.0
Positive for thyrotropin-receptor autoantibodies — no. of patients/total no. (%)	32/47 (68)	30/41 (73)	27/41 (66)
Positive for thyroid peroxidase autoantibodies — no. of patients/total no. (%)	32/47 (68)	27/41 (66)	26/41 (63)

Table 1. (Continued.)

Characteristic	Selenium (N=54)	Placebo (N=50)	Pentoxifylline (N=48)
Eye symptoms and signs§			
Proptosis — mm	19.7±2.7	19.8±2.3	20.0±2.5
Eyelid aperture — mm	11.5±1.9	11.3±1.7	11.6±2.1
Soft-tissue involvement — no. of eyes/total no. (%)			
Absent	5/108 (5)	5/100 (5)	0
Mild	64/108 (59)	65/100 (65)	52/96 (54)
Moderate	39/108 (36)	30/100 (30)	44/96 (46)
Diplopia — no. of patients (%)¶			
Absent	43 (80)	44 (88)	43 (90)
Intermittent	6 (11)	3 (6)	2 (4)
Inconstant	5 (9)	3 (6)	3 (6)
Clinical Activity Score‖			
Median	3.5	3.0	3.0
Interquartile range	3.0–4.0	2.0–4.0	2.0–5.0

* Patients were recruited at the following EUGOGO Centers: Mainz, Germany (48 patients); Thessaloniki, Greece (33); Pisa, Italy (24), Varese, Italy (20), Amsterdam (19), and Olten, Switzerland (8). Plus–minus values are means ±SD.
† Race was reported by the investigators.
‡ The antithyroid drugs used were methimazole, carbimazole, and propylthiouracil.
§ Measurements for proptosis and eyelid aperture are the average for the two eyes; soft-tissue involvement was evaluated for each eye individually.
¶ Diplopia was evaluated according to Gorman scoring, with "intermittent" indicating diplopia only when the patient is tired or awakening, "inconstant" indicating diplopia at extremes of gaze, and "constant" indicating diplopia in the primary or reading position. None of the patients had constant diplopia.
‖ The Clinical Activity Score is the sum of the single scores, ranging from 0 (no activity) to 7 (maximal activity), for each of the following items, if present: spontaneous retrobulbar pain, pain on eye movements, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle, and edema or fullness of the eyelid.[24]

(P=0.001) and the pentoxifylline group (P=0.02) but not in the placebo group (P=0.4), whereas levels of thyrotropin-receptor autoantibodies declined in all three groups (P=0.002, P=0.002, and P=0.004, respectively) (Table 2 in the Supplementary Appendix).

PRIMARY AND SECONDARY END POINTS

The mean scores on the GO-QOL questionnaire at baseline and after the intervention are shown in Table 2. According to this assessment, a score of 1, 2, or 3 is assigned to each of the eight questions in each subscale to indicate whether the limitation was marked, mild, or absent, respectively. The scores are added to obtain a raw score. The final score is calculated as follows: (raw score − 8) ÷ 16 × 100. The score ranges from a minimum of 0 (full limitation) to 100 (no limitation). An increase in the score indicates improvement and a decrease indicates worsening. A change of at least 6 points was considered a minimal clinically important difference.

The scores at baseline showed mild-to-moderate impairment in quality of life, with no significant differences among the three groups with respect to the visual-functioning and appearance scores. At 6 months, GO-QOL scores among the 53 patients treated with selenium increased from baseline by 6 or more points for visual functioning in 33 patients (62%) and for appearance in 40 patients (75%). As shown in Figure 2A, a significantly greater proportion of patients in the selenium group had an improved quality of life at 6 months, as compared with those given placebo. Moreover, the patients treated with selenium had a substantially lower rate of worsening of quality

Table 2. Graves' Orbitopathy–Specific Quality of Life (GO-QOL) Score, Clinical Activity Score, and Eye Evaluation before and after Study Treatment.*

Variable	Selenium (N=54)	Placebo (N=50)	Pentoxifylline (N=48)	P Value†	
				Selenium vs. Placebo	Pentoxifylline vs. Placebo
GO-QOL score‡					
Visual functioning					
At baseline	80.1±17.1	84.0±19.5	77.8±16.6	0.29	0.11
Change at 6 mo	8.73±17.7	−2.4±14.6	−0.21±18.0	0.001	0.52
Change at 12 mo	11.0±15.3	−1.7±18.7	−0.64±18.1	0.004	0.80
Appearance					
At baseline	74.0±19.8	79.5±18.1	75.0±18.3	0.15	0.24
Change at 6 mo	10.6±10.9	−2.6±11.7	−1.7±13.8	<0.001	0.73
Change at 12 mo	12.6±11.8	−1.6±17.1	−0.9±16.3	<0.001	0.85
Clinical Activity Score§					
Baseline				0.17	0.60
Median	3.5	3.0	3.0		
Interquartile range	3.0–4.0	2.0–4.0	2.0–5.0		
Change at 6 mo	−1.9±1.3	−0.6±1.9	−0.9±1.4	<0.001	0.24
Change at 12 mo	−2.2±1.3	−1.0±2.3	−1.4±1.6	<0.001	0.30
Eye evaluation¶					
Eyelid aperture — no. of patients (%)					
At 6 mo				0.01	0.79
Improved	20 (37)	6 (12)	7 (15)		
Unchanged	28 (52)	38 (76)	37 (77)		
Worse	6 (11)	6 (12)	4 (8)		
At 12 mo				0.03	0.54
Improved	21 (39)	10 (20)	9 (19)		
Unchanged	26 (48)	37 (74)	33 (69)		
Worse	7 (13)	3 (6)	6 (12)		
P value for 6 vs. 12 mo‖	0.92	0.36	0.64		
Soft-tissue signs — no. of patients (%)					
At 6 mo				0.04	0.02
Improved	23 (43)	16 (32)	20 (42)		
Unchanged	28 (52)	23 (46)	26 (54)		
Worse	3 (6)	11 (22)	2 (4)		
At 12 mo				0.005	0.22
Improved	31 (57)	16 (32)	20 (42)		
Unchanged	21 (39)	24 (48)	24 (50)		
Worse	2 (4)	10 (20)	4 (8)		
P value for 6 vs. 12 mo‖	0.30	0.97	0.69		

Table 2. (Continued.)

Variable	Selenium (N=54)	Placebo (N=50)	Pentoxifylline (N=48)	P Value†	
				Selenium vs. Placebo	Pentoxifylline vs. Placebo
Proptosis — no. of patients (%)					
At 6 mo				0.48	0.60
Improved	6 (11)	3 (6)	5 (10)		
Unchanged	45 (83)	42 (84)	40 (83)		
Worse	3 (6)	5 (10)	3 (6)		
At 12 mo				0.93	0.99
Improved	9 (17)	7 (14)	7 (14)		
Unchanged	39 (72)	37 (74)	35 (73)		
Worse	6 (11)	6 (12)	6 (13)		
P value for 6 vs. 12 mo‖	0.36	0.37	0.43		
Eye-muscle motility — no. of patients (%)					
At 6 mo				0.35	0.60
Improved	2 (4)	5 (10)	3 (6)		
Unchanged	50 (93)	42 (84)	40 (83)		
Worse	2 (4)	3 (6)	5 (10)		
At 12 mo				0.27	0.23
Improved	3 (6)	5 (10)	1 (2)		
Unchanged	49 (91)	40 (80)	42 (88)		
Worse	2 (4)	5 (10)	5 (10)		
P value for 6 vs. 12 mo‖	0.90	0.76	0.59		

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.

† For changes from baseline in the GO-QOL scores, comparisons of selenium with placebo and of pentoxifylline with placebo were calculated with the use of the two-sided t-test. For changes from baseline in the Clinical Activity Score, comparisons of selenium with placebo and of pentoxifylline with placebo were calculated with the use of the Mann–Whitney test. For changes from baseline in the eye evaluation, comparisons of selenium with placebo and of pentoxifylline with placebo were calculated with the use of the 3×2 chi-square test.

‡ The GO-QOL questionnaire measures the health-related quality of life of patients with this condition. Scores range from 0 (full limitation) to 100 (no limitations). The questionnaire was incompletely filled in or the score was missing for 12 patients (1 in the selenium group, 4 in the placebo group, and 7 in the pentoxifylline group).

§ The Clinical Activity Score is the sum of single scores, ranging from 0 (no activity) to 7 (maximal activity),[24] with one point given for each of the following items, if present: spontaneous retrobulbar pain, pain on eye movements, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle, or edema or fullness of the eyelid.

¶ Changes were graded according to predefined criteria as improved, unchanged, or worse, as reported in Table 1 in the Supplementary Appendix.

‖ P values were calculated with the use of the 3×2 chi-square test.

of life (9 of 53 patients) as compared with those given placebo (20 of 46 patients) (17% vs. 43%, P=0.004).

The overall ophthalmic outcome at the 6-month evaluation was significantly better in the selenium group than in the placebo group (P=0.01), whereas there was no significant difference between the pentoxifylline and placebo groups (P=0.12) (Fig. 2B). Graves' orbitopathy improved in 33 of 54 patients (61%) in the selenium group, 17 of 48 (35%) in the pentoxifylline group, and 18 of 50 patients (36%) in the placebo group; the disease worsened in 4 of 54 (7%) in the selenium group, 5 of 48 (10%) in the pentoxifylline group, and 13 of

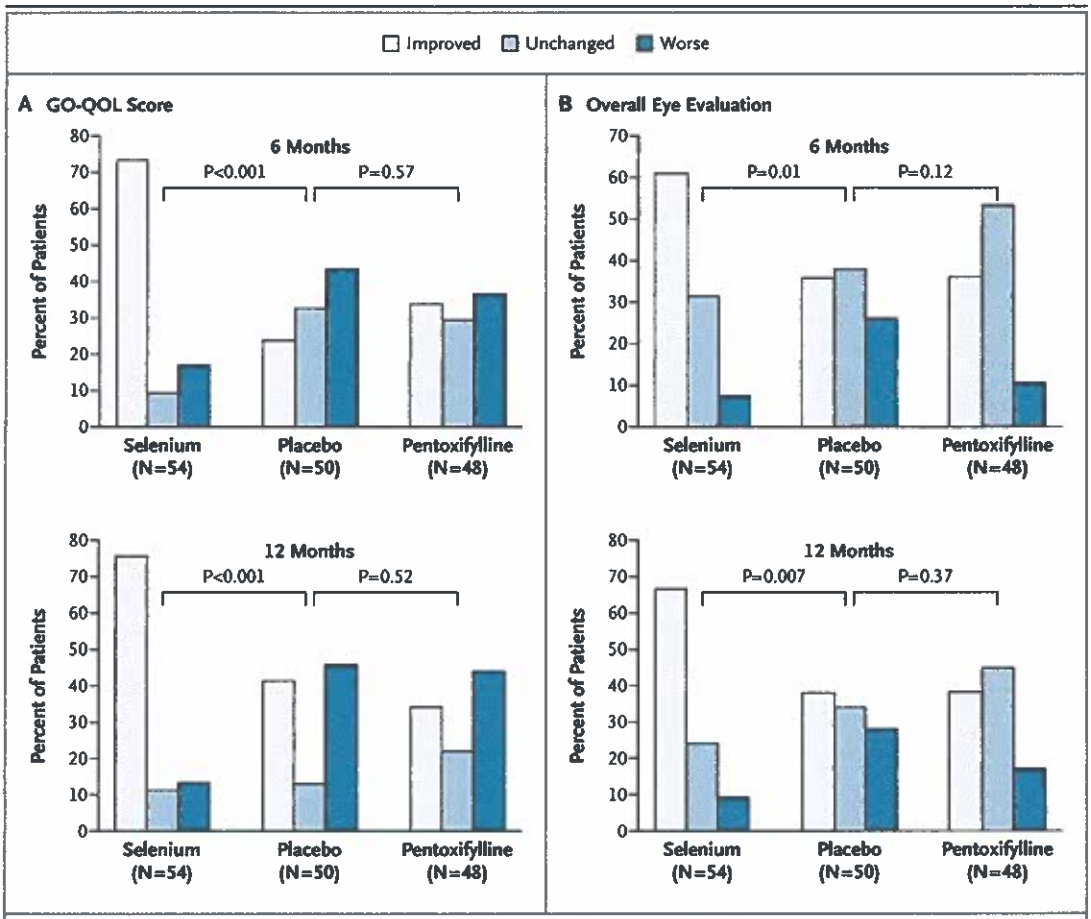

Figure 2. Primary End Points.

Panel A shows the changes reflected in the score on the Graves' orbitopathy–specific quality-of-life questionnaire (GO-QOL) at 6 months and 12 months. This questionnaire measures limitations in visual functioning (as a consequence of diplopia, decreased visual acuity, or both) and in psychosocial functioning (as a consequence of a changed appearance). Panel B shows the changes at 6 months and 12 months in overall results of the eye evaluation performed by an ophthalmologist who was unaware of the treatment assignments. The quality of life and overall eye evaluations were considered to be improved, unchanged, or worsened according to predefined criteria. Differences in proportions were tested with the use of the contingency 3×2 chi-square test.

50 patients (26%) in the placebo group. The rate of worsening of Graves' orbitopathy was significantly lower in the selenium group than in the placebo group (P=0.01). Because each of the primary outcome measurements at 6 months was significant, use of the Benjamini–Hochberg correction was not necessary. Changes in individual variables on which the overall ophthalmic outcome was based are shown in Table 2. Improvements in eyelid aperture and in soft-tissue involvement, rather than changes in proptosis and eye motility, were the major determinants of the overall ophthalmic outcome in patients treated with selenium. The median reduction in eyelid aperture was 2 mm (interquartile range, 2 to 3) at 6 months and 3 mm (interquartile range, 2 to 4) at 12 months. At 6 months, a large proportion of the 32 selenium-treated patients who had improvements in eyelid aperture, soft-tissue changes, or both also had an improvement of 6 points or more on the appearance subscale of the GO-QOL (84%; 95% confidence interval [CI], 67 to 95) and on the visual-functioning subscale (72%; 95% CI, 53 to 86) as well as in the overall score (81%; 95% CI, 63 to 93).

The beneficial effect of selenium on quality of life and the overall eye evaluation persisted for 6 months after therapy was withdrawn, and the

outcomes continued to be better in the selenium group than in the placebo group (P<0.001 for quality of life and P=0.007 for eye evaluation) (Table 3 in the Supplementary Appendix).

Visual acuity was normal in all patients at baseline and did not change during the 12-month follow-up period. Smoking status had no apparent influence on the effect of different treatments on the primary outcomes in the overall study population or in any group in the study. Extraocular-muscle dysfunction did not significantly change during the study in any group (data not shown). The mean Clinical Activity Score decreased in all groups (Table 2), and the reductions at 6 and 12 months were significantly greater in the selenium group than in the placebo group; no significant difference was observed between the pentoxifylline and placebo groups.

Table 3. Adverse Events.

Event	Selenium (N=55)	Placebo (N=52)	Pentoxifylline* (N=52)
Bloating	0	0	1
Abdominal discomfort	0	0	1
Nausea	0	0	3
Erythema	0	0	1
Pruritus	0	0	1

* Four patients left the study during the first month and were not included in the final analysis.

ADVERSE EVENTS

Drug-related adverse effects (skin and gastrointestinal disorders) occurred in seven patients who were treated with pentoxifylline (four of whom left the study during the first month). There were no drug-related adverse effects in the patients who received either selenium or placebo (Table 3).

DISCUSSION

In this study, selenium, as compared with placebo, resulted in significant improvement in the quality of life, as assessed by the GO-QOL questionnaire,[4] in patients with Graves' orbitopathy. The improvement was seen in both the appearance score and the visual-functioning score and was probably due to amelioration of soft-tissue changes and improved eyelid aperture, which occurred in most of the patients who had improved GO-QOL scores. Neither pentoxifylline nor placebo caused significant changes in quality of life.

The beneficial effect of selenium on quality of life was corroborated by a significantly better ophthalmic outcome, as compared with placebo, at the end of the 6-month treatment period. The condition improved in 33 of 54 patients, mainly owing to an amelioration of soft-tissue changes and a decrease in eyelid aperture. Four patients given selenium had mild progression of the disease that required only local measures. In the placebo group, Graves' orbitopathy improved in 18 of 50 patients and progressed in 13, 2 of whom required major interventions. Thus, as compared with placebo, selenium was associated with an increased rate of improvement but also with a decreased rate of worsening. Except for a transient benefit with respect to soft-tissue changes at 6 months, the outcomes with pentoxifylline did not differ significantly from those seen with placebo.

The Clinical Activity Score in the selenium group was significantly lower than that in the placebo group at 6 months. However, this score decreased in all three groups, probably reflecting the natural history of mild Graves' orbitopathy, which becomes less active or inactive in most cases. Exploratory evaluation at 12 months confirmed the results at 6 months.

Graves' disease is characterized by increased oxidative stress,[28,29] and the increased generation of oxygen free radicals might play a role in the pathogenesis of Graves' orbitopathy.[7-9] Serum selenoprotein P levels, an index of the oxidative state, are lower in patients with Graves' orbitopathy than in controls, with a weak inverse correlation with disease activity.[30] In contrast, a recent study showed no significant difference in selenium levels in patients with mild Graves' orbitopathy and controls.[31] Thus, we speculate that an intervention aimed at improving the antioxidant–oxidant balance might be helpful in both hyperthyroidism and Graves' orbitopathy. Antithyroid drug therapy in patients with Graves' disease decreases the generation of reactive oxygen species,[28] and euthyroidism is more rapidly reached when antioxidant supplementation (including selenium) is added to methimazole.[13] One study showed that patients with Graves' disease and remission of hyperthyroidism after antithyroid drug therapy had higher selenium concentrations than did patients with relapse, and levels of antibodies against thyrotropin receptor were negatively correlated

with serum selenium concentrations.[32] In a nonrandomized study involving patients with moderate-to-severe Graves' orbitopathy, antioxidant therapy with allopurinol and nicotinamide was shown to be beneficial as compared with placebo.[33]

Our study has two limitations. First, we do not have data on the changes in serum selenium concentrations after the administration of sodium selenite. Second, although we did not measure selenium levels in serum samples obtained before and during sodium selenite administration, most patients came from areas in which selenium levels are known to be marginally decreased in the general population.[6,34,35] As reported in other studies, the marginal selenium deficiency may have favored the beneficial effect of selenium supplementation.[6]

In summary, our data indicate that selenium supplementation for 6 months improves the course of Graves' orbitopathy and the related impairment in quality of life.

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