

ORIGINAL ARTICLE

Selenium and the Course of Mild Graves' Orbitopathy

Claudio Marcocci, M.D., George J. Kahaly, M.D.,
 Gerasimos E. Krassas, M.D., Luigi Bartalena, M.D., Mark Prummel, M.D.,*
 Matthias Stahl, M.D., Maria Antonietta Altea, M.D., Marco Nardi, M.D.,
 Susanne Pitz, M.D., Kostas Boboridis, M.D., Paolo Sivelli, M.D.,
 George von Arx, M.D., Maarten P. Mourits, M.D., Lelio Baldeschi, M.D.,
 Walter Bencivelli, Ph.D., and Wilmar Wiersinga, M.D.,
 for the European Group on Graves' Orbitopathy

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 selenium (100 μ g 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mg twice daily), or placebo (twice daily) orally for 6 months and were then followed for 6 months after treatment was withdrawn.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.)

From the Department of Endocrinology and Metabolism (C.M., M.A.A.), the Department of Neuroscience, Section of Ophthalmology (M.N.), and the Department of Internal Medicine (W.B.), University of Pisa, Pisa; and the Departments of Clinical Medicine (L. Bartalena) and Ophthalmology (P.S.), University of Insubria, Varese — both in Italy; the Departments of Medicine (G.J.K.) and Ophthalmology (S.P.), Gutenberg University Medical Center, Mainz, Germany; the Department of Endocrinology, Panagia General Hospital (G.E.K.), and the University Department of Ophthalmology, Ahepa Hospital (K.B.) — both in Thessaloniki, Greece; the Departments of Endocrinology (M.P., W.W.) and Ophthalmology (M.P.M., L. Baldeschi), Academic Medical Center, Amsterdam; and the Department of Endocrinology and Metabolism, Kantonsspital Olten (M.S.), and Interdisziplinäres Zentrum für Endokrine Orbitopathie (G.A.) — both in Olten, Switzerland. Address request reprints to Dr. Marcocci at the Department of Endocrinology and Metabolism, University of Pisa, Via Paradisa 2, 56100 Pisa, Italy, or at claudio.marcocci@med.unipi.it.

*Deceased.

This article (10.1056/NEJMoa1012985) was updated on July 28, 2011, at NEJM.org.

N Engl J Med 2011;364:1920-31.

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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 questionnaires³ 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 effects¹⁵⁻¹⁷ 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 μ g 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-

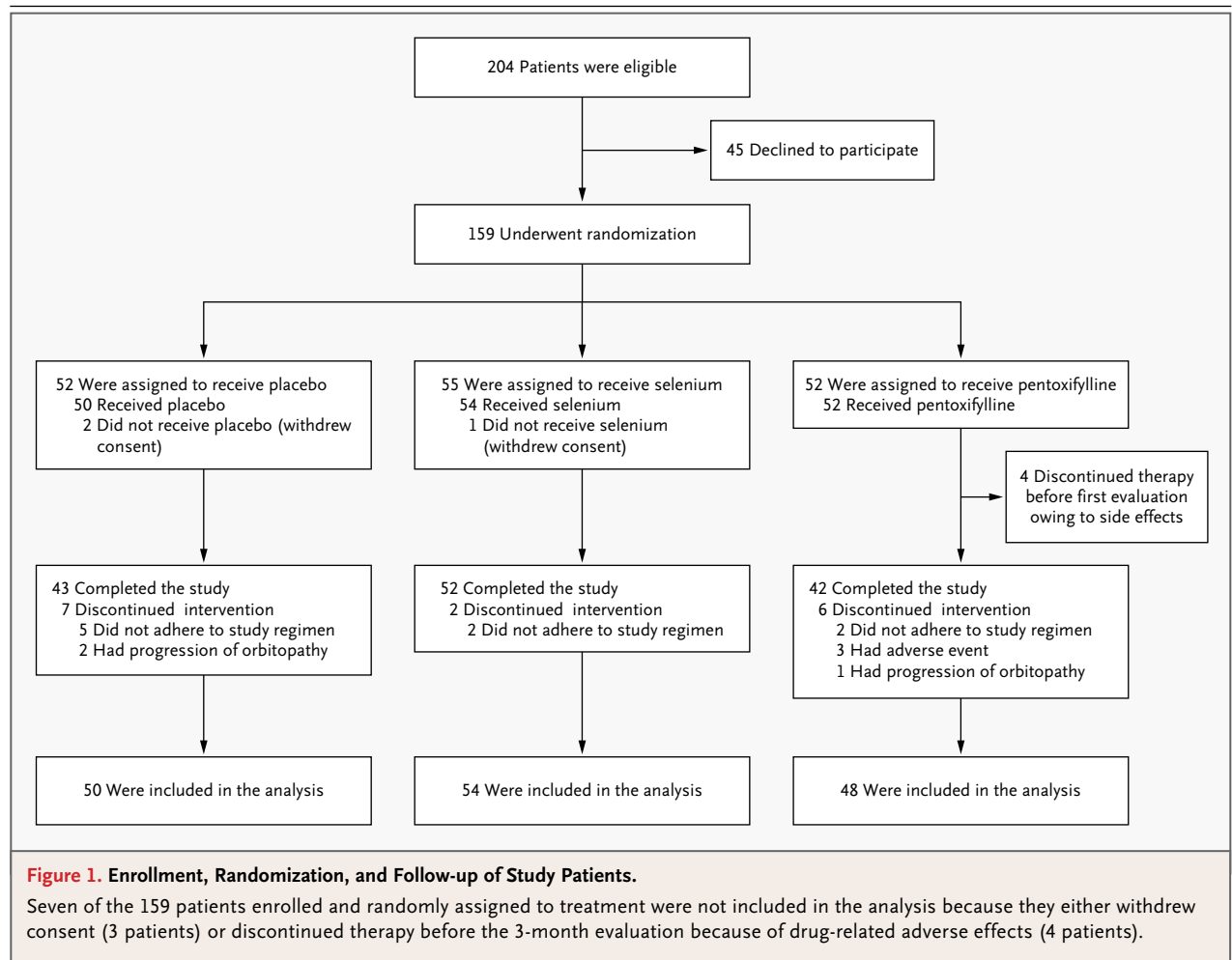
antibodies at the end of treatment (at 6 months) were compared with baseline levels with the use of the paired-sign test for thyroid peroxidase autoantibodies (since different assay methods were used at different centers) and the Wilcoxon signed-rank test for autoantibodies against the thyrotropin receptor. 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



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: $(\text{raw score} - 8) \div 16 \times 100$. The score ranges from a minimum of 0 (full limitation) to 100 (no limita-

tion). 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 $\pm$ 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 $\times$ 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.

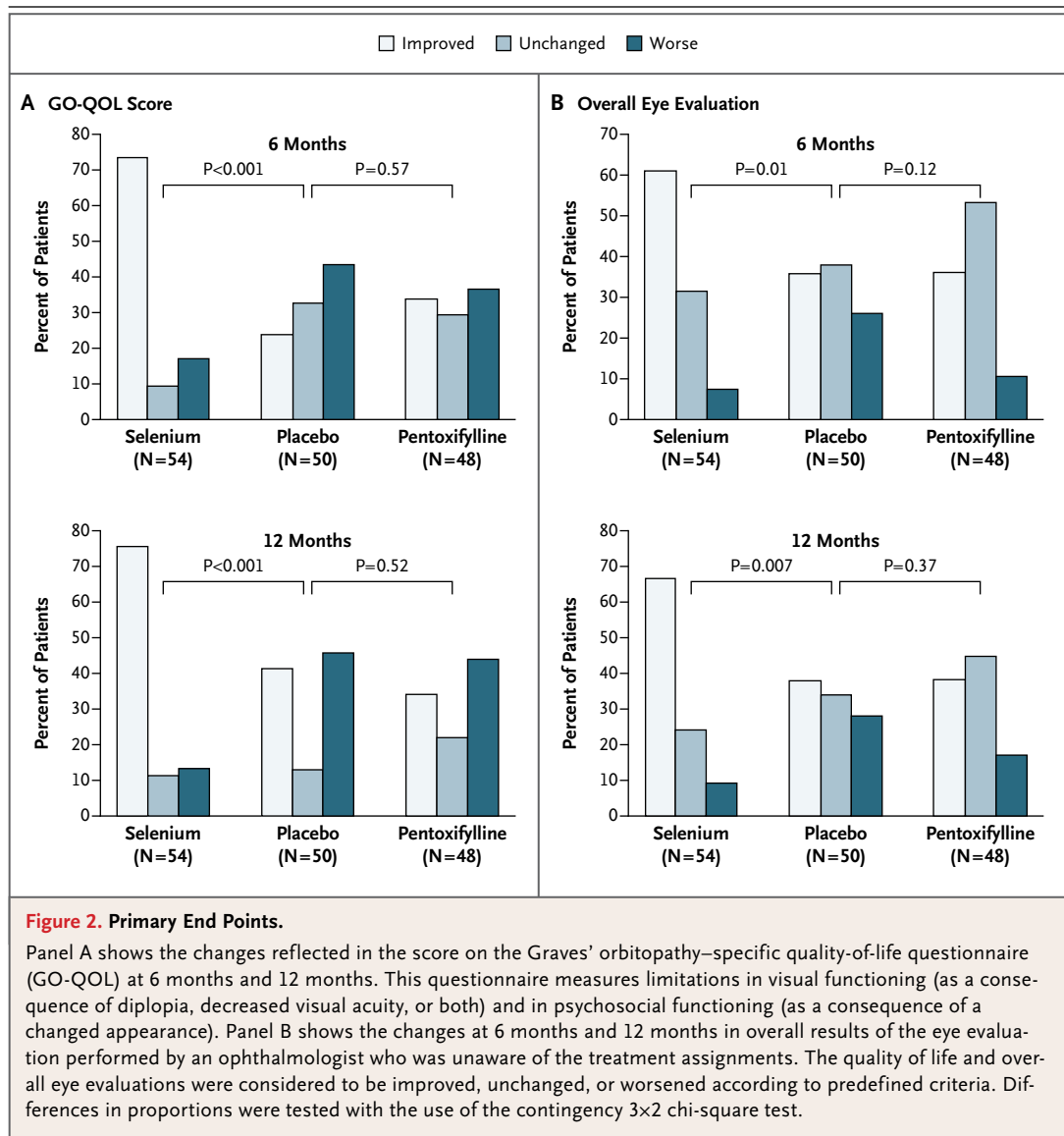
¶ Changes were graded according to predefined criteria as improved, unchanged, or worse, as reported in Table 1 in the Supplementary Appendix.

|| P values were calculated with the use of the 3 $\times$ 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 ($P=0.01$), where-as 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



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.

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 pla-

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.

cebo, 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 non-randomized 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 gen-

eral 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.

Supported by grants from the University of Pisa (Fondi d'Ateneo per la Ricerca, to Dr. Marcocci) and the Italian Ministry for Education, University and Research (PRIN 20074X8RKK, to Dr. Bartalena).

Disclosure forms provided by the authors are available at NEJM.org.

We thank Professor Jan Tyssen for his advice in preparing a revised version of the manuscript.

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