0021-972X/05/$15.00/0
*Printed in U.S.A.*

The Journal of Clinical Endocrinology & Metabolism 90(2):841–848

doi: 10.1210/jc.2004-1334

# Octreotide (Long-Acting Release Formulation) Treatment in Patients with Graves' Orbitopathy: Clinical Results of a Four-Month, Randomized, Placebo-Controlled, Double-Blind Study

J. L. Wémeau, P. Caron, A. Beckers, V. Rohmer, J. Orgiazzi, F. Borson-Chazot, M. Nocaudie, P. Perimenis, S. Bisot-Locard, I. Bourdeix, and S. Dejager

*Centre Hospitalier Universitaire (J.L.W., M.N., P.P.), 59037 Lille, France; Centre Hospitalier Universitaire Rangueil (P.C.), 31403 Toulouse, France; Centre Hospitalier Universitaire (A.B.), 400-35, Liège, Belgium; Centre Hospitalier Universitaire (V.R.), 49033 Angers, France; Centre Hospitalier Universitaire (J.O., F.B.-C.), 69495 Lyon, France; Centre Hospitalier Universitaire Saint Pierre, 1000 Bruxelles, Belgium; and Novartis Pharma SAS (S.B.-L., I.B., S.D.), 92506 Rueil Malmaison, France*

**There are few effective, safe modalities for the management of Graves' ophthalmopathy (GO), a cell-mediated immune comorbidity of thyroid disease. Somatostatin analogs inhibit lymphocyte proliferation and activation, and accumulate in the orbital tissue of patients with GO. A double-blind, placebo-controlled study of a long-acting somatostatin analog [16 wk of long-acting release formulation of octreotide (octreotide-LAR)] was conducted in 51 patients with mild active GO with the aim of preventing deterioration and precluding the need for more aggressive therapeutic modalities, such as glucocorticoids or radiotherapy. No treatment effect was observed for the primary end point (a composite parameter defining the outcome as either success or failure on the basis of changes in class/grade of the severity index and Clinical Activity Scale of GO). The Clinical Activity Scale score was reduced for patients treated with octreotide-LAR, but without any significant difference with respect to patients receiving placebo. However, octreotide-LAR significantly reduced proptosis (as measured by exophthalmometry). This was associated with nonsignificant differences in favor of octreotide-LAR in a series of proptosis-related parameters: class III grade, opening of the upper eyelid, the difference in ocular pressure between primary position and upgaze, and extraocular muscle involvement. By magnetic resonance imaging evaluation the extraocular muscle volumes appeared reduced, but nonsignificantly. No significant correlation between the initial uptake of the somatostatin analog indium-labeled and the response to treatment was observed. One patient in the octreotide-LAR group developed gallstones. In this study, octreotide-LAR did not seem suitable to mitigate activity in mild GO. Surprisingly, it significantly reduced proptosis, one of the most debilitating symptoms of GO. Additional studies are warranted to define the benefit to risk ratio of the somatostatin analogs in this indication. (*J Clin Endocrinol Metab* 90: 841–848, 2005)**

GRAVES' ORBITOPATHY (GO) is diagnosed in 10–25% of patients with Graves' disease (GD) (1, 2), although severe, debilitating forms are rarer, with only 2–5% of patients developing severe, progressive proptosis (3). However, using sensitive means, such as ultrasound, computerized tomography, or intraocular pressure measurement, evidence of extraocular infiltration can be detected in virtually all GD patients (3–5). Rather than being a complication of GD, GO is a concomitant expression of the same underlying pathological autoimmune process directed against cross-reactive autoantigens in the thyroid and retrobulbar tissues (6–8). The resultant, primarily lymphocyte-mediated, inflammatory response leads to the excessive production of glycosaminoglycans by orbital fibroblasts (2, 7, 9).

Only a weak consensus exists on either the evaluation or the management of GO. Two systems are routinely used for evaluation. The NOSPECS index (N, no signs or symptoms; O, only signs, no symptoms; S, soft tissue involvement; P, proptosis; E, extraocular muscle involvement; C, corneal involvement; S, sight loss) gives a global estimate of the severity of the various symptoms, although it has been criticized for providing only a mean assessment, so that many experts propose evaluating the various symptoms separately (10). It was partly in response to this type of criticism that Mourits *et al.* (11) developed the Clinical Activity Scale (CAS), which gives a measure of disease activity.

It is generally accepted that corticosteroids and/or orbital radiotherapy should be considered as treatments for established moderately severe to severe GO, both of which are associated with some adverse reactions (12). Moreover, a successful outcome is far from certain (7, 13, 14). There exists, therefore, a genuine need for new effective and safe modalities that can be used in the early stages of GO to prevent deterioration to a more severe form.

Somatostatin is an endogenous cyclic peptide that has broadly inhibitory activity on a variety of different systems (15). Many different cell types, including fibroblasts and lymphocytes, are known to express somatostatin receptors, and the level of expression of high affinity somatostatin

**First Published Online November 23, 2004**

Abbreviations: CAS, Clinical Activity Scale; GD, Graves' disease; GO, Graves' ophthalmopathy; MRI, magnetic resonance imaging; NMR, nuclear magnetic resonance; SstR, somatostatin receptor.

**JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

receptors in retrobulbar tissue is known to correlate with the clinical activity of GO (6). The rationale for using somatostatin analogs to treat GO is based on the putative capacity of these peptides to inhibit lymphocyte activation, proliferation, and cytokine production (16, 17). Moreover, somatostatin is known to inhibit the release of IGF, the production of which by fibroblasts has been implicated in the pathogenesis of GO (18), even if serum levels of IGF are normal in the active forms of GO, suggesting intraorbital overproduction (19). A number of preliminary open studies have suggested that somatostatin analogs might be effective against GO. In these studies the main effect of octreotide or lanreotide was the attenuation of soft tissue and extraocular muscle involvement in a majority of the patients treated (in most cases for a period of 3 months) (20–22), although in few open studies a beneficial effect was also observed on proptosis (23, 24).

However, the studies conducted to date have addressed highly disparate patient populations at different stages of the disease, they have lacked appropriate controls, and the numbers studied have been small, so any conclusions to be drawn from these studies are necessarily provisional (18). Because a significant proportion of patients with GO improve spontaneously, clinical trials designed to test the efficacy of new treatments in thyroid-associated ophthalmopathy should be scrupulously controlled to allow for the natural tendency toward remission (25).

Hence, there was a need for a randomized, placebo-controlled, double-blind study to investigate the efficacy of somatostatin analogs in the treatment of GO. In this study it was decided to use the long-acting release formulation of octreotide (octreotide-LAR) in patients with mild, active GO with the aim of preventing additional deterioration and precluding the need for more aggressive therapeutic modalities, such as glucocorticoids or radiotherapy.

## Subjects and Methods

### *Study design and objectives*

A double-blind, placebo-controlled, randomized study was conducted. Patients were recruited and treated at 13 centers (10 in France and three in Belgium). Randomization on a 1:1 basis to either octreotide-LAR or placebo was centralized and was stratified by sex and current smoking status (smoking being defined as the consumption of more than five cigarettes per day).

Between inclusion and the beginning of treatment, an 8-wk interval was programmed to confirm the stability of euthyroidism. After baseline monitoring on the first day of treatment, patients were examined at 4-wk intervals throughout the 16-wk treatment period and then again in a follow-up evaluation 6 months after the beginning of treatment. Adverse events occurring at any time in the 6-month study period were recorded and analyzed.

### *Patients*

Eligible for the study were euthyroid outpatients with clinically active, mild to moderate GO. The diagnosis of GO was based on the presence of at least two of the following signs: retraction of the eyelid (a palpebral fissure wider than 11 mm or a distance of >7 mm between the edge of the lower eyelid and the center of the pupil), palpebral edema, proptosis, and impaired ocular mobility with increased intraocular pressure on upgaze associated with enlargement of at least one oculomotor muscle. Mild to moderate disease severity was defined using the NOSPECS scale as either minimal to moderate soft tissue involvement (class 2, grades a–c) or minimal to moderate soft tissue involvement (grade 2a or b) coupled with mild proptosis (grade 3a), mild extraocular muscle involvement (grade 4a), or mild corneal involvement (grade 5a). Clinically active disease (based on eye pain, ocular or eyelid erythema, conjunctival or eyelid edema, and worsening of proptosis) was defined as a score of 3 or more on the 10-item CAS proposed by Mourits *et al.* (11). Stable euthyroidism was defined by blood concentrations of free $T_4$, free $T_3$, and TSH in the normal range throughout the study period.

Exclusion criteria included severe refractive abnormalities or any other eye problem that might interfere with the accuracy of the study measurements, gallstones, or a history of treatment within the preceding 6 months with systemic corticosteroids, immunosuppressive drugs, radiotherapy, or chemotherapy.

### *Study treatment*

Octreotide-LAR (Sandostatin LAR, supplied by Novartis, Rueil Malmaison, France) was supplied in vials containing 30 mg lyophilisate for reconstitution to a volume of 2 ml. Treatments (octreotide-LAR or placebo) were administered at 4-wk intervals over 4 months (d 0 and wk 4, 8, and 12) by im injection.

### *Concomitant medications*

Stable euthyroidism was a formal requirement in the protocol, so exogenous $T_4$ at the appropriate dosage was permitted throughout the study period, as were antithyroid drugs (carbimazole, benzylthiouracil, and propylthiouracil), as long as the dosage of the latter was not significantly modified during the study. Also permitted were topical products (artificial tears, ocular lubricants, and antibiotic eye drops). Formally excluded were radiotherapy, chemotherapy, iv immunoglobulin, immunosuppressants, anticoagulants, antiplatelet drugs, oral iodine/iodide, lithium, and amiodarone.

### *Study assessments*

The main end point was a binary success/failure criterion based on changes in NOSPECS classification and CAS between baseline (d 0) and the end of treatment (wk 16). Success was defined as a decrease in NOSPECS class or grade only when CAS was unchanged or decreased; failure was defined as either an increase in CAS or an absence of change or an increase in NOSPECS class or grade. If changes were recorded in two different NOSPECS classes, the higher change was used to define the result.

In addition to the main composite efficacy end point, in a secondary analysis the groups were compared on the basis of overall changes in CAS and in individual items of the ophthalmological examination, with special attention paid to objective parameters (notably proptosis, as measured using the Hertel exophthalmometer, and palpebral opening and retraction). Furthermore, self-assessment was evaluated with two validated quality of life questionnaires: one global, the SF-36 (26), and the other specific to GO, the GO-QOL (27).

Thyroid function (blood levels of TSH, $T_4$, and $T_3$) was monitored throughout the study period, and pertinent serological parameters (antibodies against thyroglobulin, thyroperoxidase, and the TSH receptor) were assayed at baseline and the end of treatment. All serum measurements were performed in each center with commercial kits.

Somatostatin receptor scintigraphy was performed at baseline using a $\gamma$-camera to acquire data on the anterior head and both profiles 4 and 18–24 h after the iv injection of [$^{111}$In]pentreotide (220 MBq, 10 $\mu$g; octreoscan, Mallinckrodt, St. Louis, MO). The images were centrally interpreted by two independent observers blinded to patient's data. A semiquantitative four-point score was used to classify the intensity of uptake, as previously reported (28, 29): negative scintigraphy, uptake indiscernible from background noise; ±, weakly positive scintigraphy, uptake hardly to slightly discernible from background noise at 4 or 24 h; +, moderately positive scintigraphy, moderate uptake at 4 and 24 h; and 2+, strongly positive scintigraphy, strong uptake at 4 h with enhancement at 24 h. In the event of conflicting interpretations, the two observers had to meet to agree to a consensus. The objective was to investigate the reported correlation of this parameter with the CAS (30, 31) with a view to evaluating the predictive power of this examination *vis-à-vis* the efficacy of octreotide treatment (32). In normal individuals, there is no orbital uptake of octreoscan.

Extraocular muscle involvement, an almost typical sign in GO, was specifically investigated at baseline and at month 4 by nuclear magnetic resonance (NMR) measurement of the lateral, medial, inferior, and superior rectus muscles (33–35) with a T1-weighted and a T2 gradient echo sequence. Results were read centrally by an independent expert and analyzed for correlations with other parameters, notably baseline scintigraphic data and CAS, antibody titers, and outcome.

For the safety analysis, details of all adverse events occurring at any time in the 6-month study period were collected.

### *Sample size and statistical analysis*

Assuming a success rate of 30% in the placebo group and a difference of 35% in the treated group compared with placebo, it was calculated that 37 patients/treatment group had to be recruited to guarantee a power of 0.80. However, due to the very slow recruitment, the study had to be stopped after 51 patients had been randomized (inclusion duration of 18 months).

The main efficacy analysis was based on the intention to treat population (all patients who received at least one dose of the test treatment and for whom pretreatment and end of treatment data were available for at least one efficacy parameter) and comparison of the baseline reading with the last measurement during treatment. Parallel analyses conducted on the per protocol population gave similar results. All statistical analyses were two-sided, with a critical significance level of 5%. For the main end point, the effect of treatment was analyzed using the Mantel Haenszel test adjusted for sex and smoking status. Because stratification of randomization according to sex and smoking resulted in unbalanced distribution between the two groups at certain centers, no center-adjusted analysis was attempted. For the secondary end points discussed, changes in the two groups between baseline and the end of either treatment or follow-up were compared using the Wilcoxon two-sample test. All relevant ophthalmological parameters were evaluated for both eyes and were analyzed in two ways: the mean of both eyes, and with respect to the most severely affected eye at baseline (as defined by the exophthalmometer measurement). Frequency tables were compiled for adverse events, classified according to the standard WHO-ART Body System Dictionary and preferred terms. All laboratory results out of the normal range were listed.

### *Ethics*

All patients gave written, informed consent to participate, after having been judged able to understand and comply with the requirements of the study, which was conducted in accordance with the Helsinki Declaration concerning medical research on human subjects (as amended) and European Union Directive 91/507/EC. The protocol was preapproved by the ethics committee of Lille University Hospital.

## Results

### *Population*

Enrolment began in January 2001, with the last patient completing final evaluation in June 2003. Fifty-one patients were recruited. The patient populations are described in Table 1.

### *Demographic and background characteristics*

The study population was representative of the GO population with respect to all key parameters, namely gender, age, body weight, and the preponderance of GD of recent onset. The orbitopathy in this population was of relatively long standing (Table 2), but was still active (CAS, ≥3; mean, 4.2 ± 1.6). As shown in Table 2, the stratified centralized randomization process generated two broadly comparable treatment groups. There were no significant differences between the two groups.

**TABLE 1.** Study populations

| | Octreotide-LAR | Placebo | Total |
|---|---|---|---|
| Randomized (tolerance) | 26 | 25 | 51 |
| Intention to treat | 25[a] | 25 | 50 |
| Per protocol | 18 | 22 | 40 |
| Major protocol violations | 7 | 3 | 10 |
| Unstable thyroid function[b] | 4 | 0 | 4 |
| Other | 3[c] | 3[d] | 6 |
| Premature withdrawal | 2 | 2 | 4 |
| Insufficient efficacy | 1 | 1 | 2 |
| Other | 1[e] | 1[f] | 2 |

[a] Inadequate efficacy data for one patient who withdrew from the study after one dose of octreotide-LAR.
[b] TSH level of greater than 10 IU/ml detected at some point in the study period.
[c] NOSPECS grade outside of stipulated range/CAS too low/end of treatment monitoring outside of stipulated time frame.
[d] NOSPECS grade outside of stipulated range/no baseline ophthalmologic examination data.
[e] Due to an adverse event.
[f] Due to administrative problems.

### *Efficacy*

No significant treatment effect emerged from the analysis of the main composite efficacy end point (Table 3) regardless of whether the analysis was conducted on the intention to treat or the per protocol population. Considering the components of the primary end point independently, a small improvement was observed in CAS for patients treated with octreotide-LAR and also in the group receiving placebo, without any significant difference between the two groups. No significant change was detected in either group in any of the following ophthalmological parameters: palpebral edema, oculomotor function, tear secretion, diplopia, ophthalmoscopy findings, and intraocular pressure. There was a marginal tendency toward diminished soft tissue involvement, but this was not associated with any difference between groups (not shown).

However, a stronger tendency toward reduction was observed in the octreotide-LAR group in the proptosis component of the NOSPECS classification in the form of a downward shift in grade between baseline and the end of treatment, with no such change recorded in the control group. Furthermore, this trend persisted posttreatment. A decrease of 2 mm or more in proptosis was observed in one patient in each group at the end of the 4-month treatment period and in four patients in the octreotide-LAR group, but in only one patient in the placebo group at the end of the study, *i.e.* 2 months posttreatment. Moreover, the apparent improvement was statistically significant as observed in the quantitative exophthalmometric measurements in the patient groups. Proptosis was decreased by the end of the treatment period in the octreotide-LAR group, whereas no change was measured in the placebo group. The difference between the groups was significant whether the analysis was carried out on the mean of both eyes ($P = 0.027$) or the most severely affected eye alone ($P = 0.014$). These data for the most severely affected eye are presented in Fig. 1. A nonsignificant, but parallel, change was detected in a related parameter, namely, the opening of the upper eyelid, which decreased from 0.4 to 0.1 mm in the octreotide-LAR group, but increased from 0.6 to 0.7 mm in the placebo group.

**TABLE 2.** Demographic and background characteristics of the randomized population

| | Octreotide-LAR (n = 26) | Placebo (n = 25) | Total (n = 51) |
|---|---|---|---|
| Sex [no. (%)] | | | |
| M | 6 (23.1) | 4 (16.0) | 10 (19.6) |
| F | 20 (76.9) | 21 (84.0) | 41 (80.4) |
| Age (yr), mean ± SD | 47.5 ± 12.3 | 47.1 ± 12.6 | 47.3 ± 12.3 |
| Height (cm), mean ± SD | 162 ± 7 | 165 ± 9 | 164 ± 8 |
| Weight (kg), mean ± SD | 63.5 ± 12.8 | 65.3 ± 15.6 | 64.4 ± 14.1 |
| Smoking status, [no. (%)] | | | |
| Nonsmokers | 9 (34.6) | 12 (48.0) | 21 (41.2) |
| Former smokers | 6 (23.1) | 6 (24.0) | 12 (23.5) |
| Current smokers[a] | 11 (42.3) | 7 (28.0) | 18 (35.3) |
| Nature of thyroid disease | | | |
| GD [no. (%)] | 25 (96.2) | 24 (96.0) | 49 (96.1) |
| History in months [mean ± SD (range)] | 29.0 ± 27.02 (4–101) | 30.6 ± 39.76 (5–165) | 29.8 ± 33.51 |
| Hashimoto's disease [no. (%)] | 1 (3.8) | 2 (8.0) | 3 (5.9) |
| History | 303 | 32 and 118 | 151.0 ± 138.48 |
| History of GO in months, mean ± SD | 19.8 ± 22.1 | 22.1 ± 32.3 | 21.0 ± 27.3 |
| [range, median] | [3–80, 12.0] | [3–165, 11.0] | |
| Treatment for thyroid disease [no. (%)] | | | |
| Concomitant | | | |
| None | 1 (3.8) | 2 (8.0) | 3 (5.9) |
| Antithyroid drugs | 15 (57.7) | 16 (64.0) | 31 (60.8) |
| $T_4$ | 21 (80.8) | 19 (76) | 40 (78.4) |
| Previous treatment | | | |
| None | 2 (7.7) | 7 (28.0) | 9 (17.6) |
| Thyroidectomy | 4 (15.4) | 4 (16) | 8 (15.7) |
| Antithyroid drugs | 20 (76.9) | 14 (56) | 34 (66.7) |
| Iodine [$^{131}$I] | 4 (15.4) | 0 | 4 (7.8) |

[a] Consumption of more than five cigarettes per day.

**TABLE 3.** Efficacy parameters (intention-to-treat population)

| | Octreotide-LAR | Placebo | $P^a$ |
|---|---|---|---|
| Primary (composite success/failure) end point | | | |
| End of treatment[b] | (n = 25) | (n = 25) | |
| Success [no. (%)] | 7 (28.0) | 11 (44.0) | 0.30 |
| Failure [no. (%)] | 18 (72.0) | 14 (56.0) | |
| End of study | (n = 24) | (n = 24) | |
| Success [no. (%)] | 9 (37.5) | 11 (45.8) | 0.50 |
| Failure [no. (%)] | 15 (62.5) | 13 (54.2) | |
| | | | $P^c$ |
| Selected secondary end points | | | |
| CAS | | | |
| Baseline | 4.2 ± 1.61[d] | 4.5 ± 1.26[d] | |
| End of treatment[b] | 3.1 ± 1.7[d] | 3.4 ± 1.9[d] | 0.80 |
| End of study | 2.5 ± 1.1[e] | 3.2 ± 2.5[e] | 0.94 |
| Proptosis (mm) | | | |
| Mean for both eyes | | | |
| Baseline | 21.1 ± 1.92[d] | 20.3 ± 1.96[d] | |
| End of treatment[b] | 20.7 ± 2.19[d] | 20.5 ± 2.03[d] | 0.027 |
| End of study | 20.3 ± 1.97 | 20.3 ± 2.13 | 0.18 |
| Most severely affected eye[f] | | | |
| Baseline | 21.4 ± 2.09[d] | 20.7 ± 1.92[d] | |
| End of treatment[b] | 20.6 ± 2.28[d] | 20.7 ± 2.23[d] | 0.014 |
| End of study | 20.6 ± 2.14[e] | 20.5 ± 2.34[e] | 0.17 |
| | Octreotide-LAR | Placebo | |
| NOSPECS proptosis profile | | | |
| Baseline→end of treatment→end of study | 0: 36%→48%→50% | 0: 24%→24%→29.2% | |
| | A: 56%→40%→44% | A: 68%→64%→62.5% | |
| | B: 8%→12%→4.2% | B/C: 8%→12%→ 8.4% | |

[a] Mantel Haenszel test stratified by sex and smoking status to compare with difference *vis-à-vis* baseline.
[b] End of treatment; last measurement during treatment (after 12 or 16 wk of treatment).
[c] Wilcoxon two-sample test to compare with difference *vs.* baseline.
[d] n = 25.
[e] n = 24.
[f] That with the higher exophthalmometer reading at baseline.

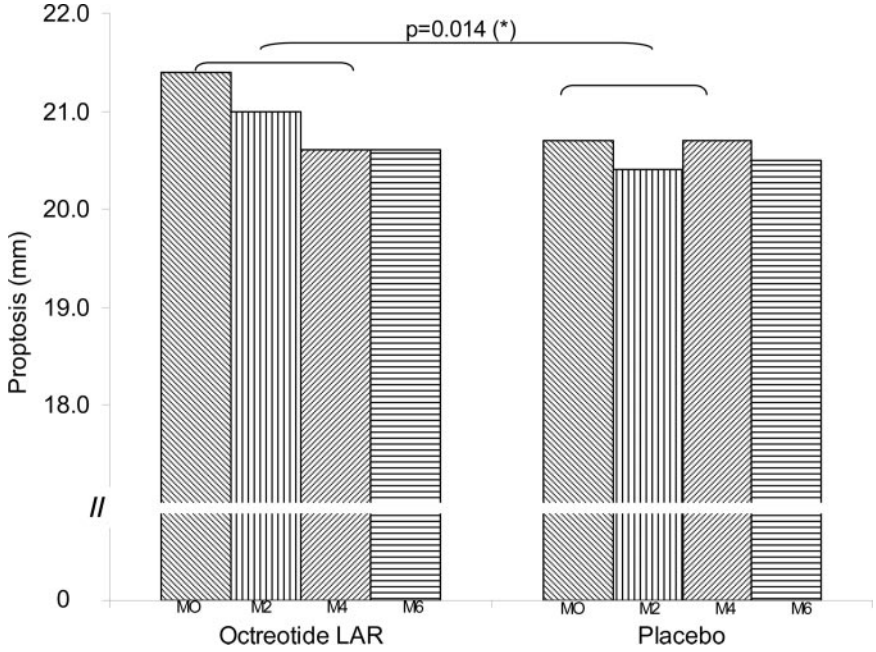


FIG. 1. Mean proptosis value for the worst eye at inclusion (M0), 2 months (M2), and 4 months (M4) of treatment period and 2 months after the end of the therapy (M6). *, Wilcoxon's rank-sum test between treatment groups at the end of treatment.

Furthermore, the difference in ocular pressure between the primary and upgaze positions was slightly improved after 16 wk of treatment (from 2.8 to 2.7 mm Hg), whereas it deteriorated over the same period in the placebo group (from 3.9 to 4.3 mm Hg).

Extraocular muscular involvement was directly addressed by NMR measurement of the lateral, medial, inferior, and superior rectus muscles at baseline and at the end of treatment. The presence of at least one muscle with T2 gradient echo sequence hypersignal, a parameter related to inflammation, was found at baseline in only seven of 25 patients in both octreotide-LAR and placebo groups. Over the course of octreotide-LAR treatment, the frequency of T2 hypersignal diminished in the treated group in all four muscles (inferior, 25% to 20.8%; lateral, 16.7% to 4.2%; median, 25% to 20.8%; superior, 20.8% to 12.5%), whereas no such consistent change was observed in the placebo group. A global overview, obtained by calculating the total surface areas for the four muscles using the equation (length + height)$^2$/16 $\times$ 3.14, illustrates the slight, but nonsignificant, improvement induced by octreotide-LAR (220 $\pm$ 39 to 181 $\pm$ 15 mm$^2$; $P >$ 0.05; Fig. 2). No significant changes were observed in self-assessment with either the SF-36 questionnaire or the GO-QOL questionnaire.

*Predictive value of somatostatin receptor scintigraphy and magnetic resonance imaging (MRI)*

The semiquantitative results of orbital [$^{111}$In]pentetreotide uptake did not show any significant correlation with the baseline CAS (r = 0.21; $P$ = 0.147), nor was any correlation observed between the strength of the initial signal and the response to treatment (Table 4). It is worth noting that 46% of the patients in the octreotide-LAR group and 40% in the placebo group produced no signal. Baseline MRI detected a T2 hypersignal in only seven of 25 patients in both octreotide-LAR and placebo groups. The presence of T2 hypersignal correlated significantly with [$^{111}$In]pentetreotide uptake ($P$ = 0.032); there was also some, but a nonsignificant, correlation with the CAS (mean score, 5.00 $\pm$ 2.08 in the T2$^+$ patients *vs.* 4.09 $\pm$ 1.04 in the T2$^-$ patients; $P$ = 0.21).

*Thyroid function and serology*

The levels of TSH and free $T_4$ remained stable in both groups throughout the study period. The level of antibodies directed against the TSH receptor decreased significantly in both groups ($P <$ 0.005), with no significant difference between the groups ($P$ = 0.35). Antibody levels did not correlate with any inflammatory parameter related to disease activity (CAS or MRI T2 signal).

*Safety*

Octreotide-LAR induced the expected profile of minor side-effects: essentially temporary, mild gastrointestinal perturbations (diarrhea, abdominal pain, nausea, and constipa-

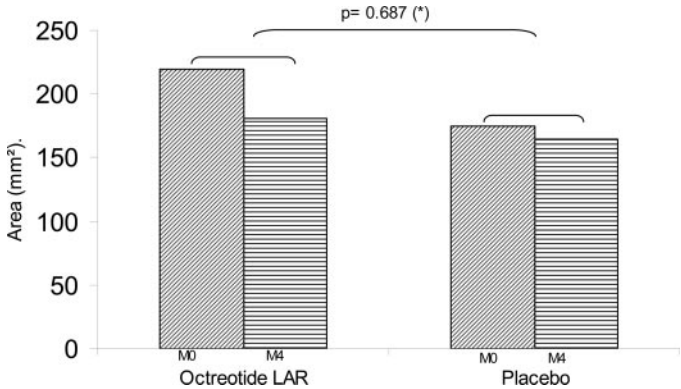


FIG. 2. Total muscle area for the eye with the more severe baseline exophthalmos at inclusion (M0) and after 4 months (M4). Muscle area is derived from NMR evaluation. *, Wilcoxon's rank-sum test between treatment groups on change from baseline.

**TABLE 4.** Predictive value of somatostatin receptor scintigraphy (SRS) *vis-à-vis* the efficacy of octreotide

| Baseline SRS signal | Outcome | Octreotide-LAR (n = 24) | Placebo (n = 25) |
|---|---|---|---|
| Negative[a] | Success | 4 (16.8) | 4 (16.0) |
| | Failure | 7 (29.2) | 6 (24.0) |
| Weakly positive[b] | Success | 2 (8.3) | 2 (8.0) |
| | Failure | 3 (12.5) | 3 (12.0) |
| Moderately positive[c] | Success | 0 | 5 (20.0) |
| | Failure | 2 (8.3) | 5 (20.0) |
| Strongly positive[d] | Success | 1 (4.2) | 0 |
| | Failure | 5 (20.8) | 0 |

Values are the number of subjects (percentage).
[a] Negative: uptake indiscernible from background noise.
[b] Weakly positive: uptake hardly to slightly discernible from background noise at 4 or 24 h.
[c] Moderately positive: Moderate uptake at 4 and 24 h.
[d] Strongly positive: strong uptake at 4 h with enhancement at 24 h.

tion). Nevertheless, a serious adverse event attributed to the treatment was one case of gallstones that was confirmed on coelioscopic cholecystectomy; the pretreatment ultrasound examination carried out on this patient 9 months before the study had revealed no abnormality.

## Discussion

In this placebo-controlled, double-blind study of the efficacy of octreotide-LAR in the treatment of mildly active GO, no significant effect of somatostatin analog treatment was detected for the main efficacy end point, a composite parameter in which success is defined by decreased disease severity coupled with unchanged or decreased disease activity.

Mention should be made of possible bias in the study. 1) There were more active smokers in the octreotide-LAR than in the placebo group. 2) More patients in the placebo group had not received any form of treatment in the past for GD, suggesting that their disease might have been of more recent onset. 3) Four patients in the octreotide-LAR group had been previously treated with radioactive iodine compared with none in the placebo group. 4) As a result of different strategies for the management of GD in the various centers, the protocol requirement for stable euthyroidism throughout the duration of the study was violated for a short while in four cases, all in the octreotide-LAR group. All of these factors are known to exacerbate GO or compromise the outcome of treatment: smoking (36, 37), stage of disease (38), iodine radiotherapy (39), and unstable thyroid function (25). Furthermore, the disease was of relatively long standing in those patients with a mean history of almost 2 yr and a median of 12 months. Probably the longer the duration of GO, the weaker the inflammatory activity of the disease (40). Although a CAS of more than 3 was a prerequisite for inclusion, the fact that a large proportion of the patients in both groups may have been at a relatively late stage of the disease is also supported by both the baseline scintigraphic data, with 43% of the patients giving a completely negative signal, and the T2-weighted MRI scan results, with only 28% of patients giving a positive signal at the beginning of the study.

Although correlation has been reported between [$^{111}$In] pentetreotide uptake and the presence of a MRI T2 hypersignal, we failed to observe any such correlation between uptake and either baseline CAS (21, 32, 41) or response to treatment with somatostatin analogs (42). In previous studies the populations were probably at a more active stage of the disease, as evidenced by scintigraphic data (29).

Somatostatin is a pleiotropic effector molecule with characterized effects on thyroid function (43). In this study no significant differences were observed between the treated and control groups in a variety of parameters of thyroid function, notably the concentrations of $T_4$, T3, and TSH in the blood. Predictably, no effects of octreotide-LAR on thyroid function could be detected in this study, due to the stronger effects of the antithyroid drugs. Moreover, levels of antibodies directed against the TSH receptor decreased in a significant fashion in both groups, with no difference observed between them. In contrast to a prior observation (6), there was no correlation between antibody levels and any of the inflammatory parameters related to disease activity (CAS or MRI T2 signal).

Despite the lack of any difference between the two groups with respect to the main efficacy end point, a significant effect of treatment was observed in one key symptom of GO, namely proptosis. Proptosis, which is particularly amenable to objective measurement, was mildly decreased in the treated group, but not in untreated patients. The effect at the end of treatment was statistically significant for both the mean of the two eyes and the most severely affected eye alone, and the improvement was sustained through 2 months after the end of treatment. In a study such as this in which a great number of different individual variables are tested (with the ophthalmological examination alone generating five objective variables and five other analyzable variables), the dangers of multiple testing are an important issue (44). If 10 variables are tested with a critical significance level of 5%, it is likely that a significant difference will be observed in at least one of them even if the null hypothesis is true. However, in this study strong circumstantial evidence that the beneficial effect of treatment on proptosis is indeed a real one is provided by the concordance of a whole series of results for other, closely related parameters, namely NOSPECS class III grade, opening of the upper eyelid, and the difference in ocular pressure between primary position and upgaze. Furthermore, MRI dimensioning detected a tendency toward diminished soft tissue involvement, the process that underlies proptosis, during and after octreotide-LAR treatment. The total area corresponding to the cumulate surface of the intraorbital muscles was reduced, but not significantly. This suggests that the reduction of proptosis arose from a reduction of both muscular and adipose intraorbital contents.

None of these other individual differences is significant, but all are in the same direction, pointing to real therapeutic efficacy *vis-à-vis* proptosis, one of the most clinically significant symptoms of GO and certainly the most debilitating in cosmetic and, therefore, psychological terms. In agreement with these data, the double-blind, placebo-controlled trial of octreotide-LAR in thyroid-associated orbitopathy conducted in Great Britain and Germany also mentioned a modest benefit of the somatostatin analog, but it was only significant on exophthalmos (45). The slight effectiveness of octreotide-

LAR might be dependent upon its restricted specificity [somatostatin receptor 2 (SstR2) and SstR5]. Because other SstR subtypes are also expressed in resident and infiltrating cells in the orbit of GO patients (17), the potentiality of new universal analogs, such as SOM 230, has to be tested in this condition (46).

No consensus exists on the most clinically relevant parameters for the evaluation of GO, a lack the multicenter European Group on Graves' Orbitopathy is bound to correct (47). Pertinently, one of the findings of the first large-scale review conducted by this group is that the severity of proptosis tends to be underestimated in the current NOSPECS classification system, with class 3 signs found in only 38% of patients, reflecting the ill-chosen proptosis cut-off point of 23 mm. The upper limit of normal proptosis values in Caucasians is 19 mm (mean ± SD), and 63% of our patients had Hertel readings of 21 mm or greater, suggesting that the current NOSPECS classification underestimates the severity of this sign. Thus, in our study perhaps the primary end point was ill chosen, but the European Group on Graves' Orbitopathy work may lead to the definition of more pertinent criteria. Nevertheless, the solid, sustained effect on proptosis of just 16 wk of octreotide-LAR treatment is an encouraging preliminary result in light of the serious lack of therapeutic options for this condition. Future larger-scale studies are needed to confirm these results and to generate complete data on the risk to benefit ratio of the somatostatin analogs in this indication.

## Acknowledgments

We acknowledge the following individuals: Lille: B. Pertuzon and J. C. Hache; Toulouse: M. Cogne, P. Arrue, P. Imbert, and F. Courbon; Lyon: X. Ducottet, Y. Carrillon, A. Hullo, and C. Houzard; Angers: D. Duquesne, J. Bigorgne, and H. Rakotonina; Rouen: J. M. Kuhn, A. F. Cailleux, and P. Vera; Montpellier: L. Baldet, I. Raingeard, P. Tharouel, H. Collet, and C. Eliaou; Strasbourg: J. L. Schlienger, A. Bogorin, A. Constantinesco, and M. Schraub; Nancy: G. Werhya, M. Braun, P. Oliver, and J. Maalouf; Reims: B. Delemer, F. Bonnet, C. Schvartz, and A. Ducasse; Paris: F. Duron, L. Arrive, C. Nguyen, and O. Touzeau; Limoges: F. Archambeaud, A. Maubon, J. C. Vandroux, and J. P. Adenis; Liege: D. Betea and C. Andris; Brussels: D. Glinoer and C. Daumerie; and Novartis: P. Sassano and N. Febvre.

Received July 9, 2004. Accepted November 12, 2004.

Address all correspondence and requests for reprints to: Prof. J. L. Wémeau, Clinique Endocrinologique Marc Linquette, Centre Hospitalier Régional Universitaire, 59037 Lille Cedex, France. E-mail: jl-wemeau@chru-lille.fr.

This work was supported by Novartis Pharma SAS.

## References

1. **Burch HB, Wartofsky L** 1993 Graves' ophthalmopathy: current concepts regarding pathogenesis and management. Endocr Rev 14:747–793
2. **Prabhakar BS, Bahn RS, Smith TJ** 2003 Current perspective on the pathogenesis of Graves' disease and ophthalmopathy. Endocr Rev 24:802–835
3. **Bahn RS** 2003 Clinical review 157: pathophysiology of Graves' ophthalmopathy: the cycle of disease. J Clin Endocrinol Metab 88:1939–1946
4. **Amino N, Yuasa T, Yabu Y, Miyai K, Kumahara Y** 1980 Exophthalmos in autoimmune thyroid disease. J Clin Endocrinol Metab 51:1232–1234
5. **Werner SC, Coleman DJ, Franzen LA** 1974 Ultrasonographic evidence of a consistent orbital involvement in Graves's disease. N Engl J Med 290:1447–1450
6. **Gerding MN, van der Meer JW, Broenink M, Bakker O, Wiersinga WM, Prummel MF** 2000 Association of thyrotrophin receptor antibodies with the clinical features of Graves' ophthalmopathy. Clin Endocrinol (Oxf) 52:267–271
7. **Wiersinga WM, Prummel MF** 2001 Pathogenesis of Graves' ophthalmopathy: current understanding. J Clin Endocrinol Metab 86:501–503
8. **Ludgate M, Baker G** 2002 Unlocking the immunological mechanisms of orbital inflammation in thyroid eye disease. Clin Exp Immunol 127:193–198
9. **Bahn RS, Heufelder AE** 1993 Pathogenesis of Graves' ophthalmopathy. N Engl J Med 329:1468–1475
10. **Gorman CA** 1991 Clever is not enough: NOSPECS is form in search of function. Thyroid 1:353–355
11. **Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, Van der GR**1989 Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. Br J Ophthalmol 73:639–644
12. **Perros P, Kendall-Taylor P** 2002 Medical treatment for thyroid-associated ophthalmopathy. Thyroid 12:241–244
13. **Krassas GE, Heufelder AE** 2001 Immunosuppressive therapy in patients with thyroid eye disease: an overview of current concepts. Eur J Endocrinol 144: 311–318
14. **Prummel MF, Mourits MP, Blank L, Berghout A, Koornneef L, Wiersinga WM** 1993 Randomized double-blind trial of prednisone versus radiotherapy in Graves' ophthalmopathy. Lancet 342:949–954
15. **Weckbecker G, Lewis I, Albert R, Schmid HA, Hoyer D, Bruns C** 2003 Opportunities in somatostatin research: biological, chemical and therapeutic aspects. Nat Rev Drug Discov 2:999–1017
16. **Pasquali D, Vassallo P, Esposito D, Bonavolonta G, Bellastella A, Sinisi AA** 2000 Somatostatin receptor gene expression and inhibitory effects of octreotide on primary cultures of orbital fibroblasts from Graves' ophthalmopathy. J Mol Endocrinol 25:63–71
17. **Pasquali D, Notaro A, Bonavolontá G, Vassallo P, Bellastella A, Sinisi AA** 2002 Somatostatin receptor genes are expressed in lymphocytes from retroorbital tissues in Graves' disease. J Clin Endocrinol Metab 87:5125–5129
18. **Krassas GE** 1998 Somatostatin analogues in the treatment of thyroid eye disease. Thyroid 8:443–445
19. **Krassas GE, Pontikides N, Kaltsas T, Dumas A, Frystyk J, Chen JW, Flyvbjerg A** 2003 Free and total insulin-like growth factor (IGF)-I, -II, and IGF binding protein-1, -2, and -3 serum levels in patients with active thyroid eye disease. J Clin Endocrinol Metab 88:132–135
20. **Krassas G, Kaltsas T, Pontikides N, Dumas A** 1997 Somatostatin therapy and Graves' ophthalmopathy. Thyroid 7:489
21. **Krassas GE, Doumas A, Kaltsas T, Halkias A, Pontikides N** 1999 Somatostatin receptor scintigraphy before and after treatment with somatostatin analogues in patients with thyroid eye disease. Thyroid 9:47–52
22. **Kung AW, Michon J, Tai KS, Chan FL** 1996 The effect of somatostatin versus corticosteroid in the treatment of Graves' ophthalmopathy. Thyroid 6:381–384
23. **Uysal AR, Corapcioglu D, Tonyukuk VC, Gullu S, Sav H, Kamel N, Erdogan G** 1999 Effect of octreotide treatment on Graves' ophthalmopathy. Endocr J 46:573–577
24. **Ozata M, Bolu E, Sengul A, Tasar M, Beyhan Z, Corakci A, Gundogan MA** 1996 Effects of octreotide treatment on Graves' ophthalmopathy and circulating sICAM-1 levels. Thyroid 6:283–288
25. **Perros P, Crombie AL, Kendall-Taylor P** 1995 Natural history of thyroid associated ophthalmopathy. Clin Endocrinol (Oxf) 42:45–50
26. **Leplege A, Ecosse E, Verdier A, Perneger TV** 1998 The French SF-36 Health Survey: translation, cultural adaptation and preliminary psychometric evaluation. J Clin Epidemiol 51:1013–1023
27. **Terwee CB, Gerding MN, Dekker FW, Prummel MF, van der Pol JP, Wiersinga WM** 1999 Test-retest reliability of the GO-QOL: a disease-specific quality of life questionnaire for patients with Graves' ophthalmopathy. J Clin Epidemiol 52:875–884
28. **Forster GJ, Krummenauer F, Nickel O, Kahaly GJ** 2000 Somatostatin-receptor scintigraphy in Graves' disease: reproducibility and variance of orbital activity. Cancer Biother Radiopharm 15:517–525
29. **Nocaudie M, Bailliez A, Itti E, Bauters C, Wemeau JL, Marchandise X** 1999 Somatostatin receptor scintigraphy to predict the clinical evolution and therapeutic response of thyroid-associated ophthalmopathy. Eur J Nucl Med 26: 511–517
30. **Gerding MN, van der Zant FM, van Royen EA, Koornneef L, Krenning EP, Wiersinga WM, Prummel MF** 1999 Octreotide-scintigraphy is a disease-activity parameter in Graves' ophthalmopathy. Clin Endocrinol (Oxf) 50:373–379
31. **Postema PT, Krenning EP, Wijngaarde R, Kooy PP, Oei HY, van den Bosch WA, Reubi JC, Wiersinga WM, Hooijkaas H, van der LT** 1994 [$^{111}$In-DTPA-D-Phe1] octreotide scintigraphy in thyroidal and orbital Graves' disease: a parameter for disease activity? J Clin Endocrinol Metab 79:1845–1851
32. **Moncayo R, Baldissera I, Decristoforo C, Kendler D, Donnemiller E** 1997 Evaluation of immunological mechanisms mediating thyroid-associated ophthalmopathy by radionuclide imaging using the somatostatin analog $^{111}$In-octreotide. Thyroid 7:21–29
33. **Firbank MJ, Harrison RM, Williams ED, Coulthard A** 2001 Measuring extraocular muscle volume using dynamic contours. Magn Reson Imaging 19:257–265
34. **Hiromatsu Y, Kojima K, Ishisaka N, Tanaka K, Sato M, Nonaka K, Nishimura H, Nishida H** 1992 Role of magnetic resonance imaging in thyroid-associated ophthalmopathy: its predictive value for therapeutic outcome of immunosuppressive therapy. Thyroid 2:299–305
35. **Markl AF, Hilbertz T, Mann K** 1989 Graves' ophthalmopathy: standardized evaluation of computed tomography examinations; magnetic resonance imaging. Dev Ophthalmol 20:38–50

36. **Prummel MF, Wiersinga WM** 1993 Smoking and risk of Graves' disease. JAMA 269:479–482
37. **Bartalena L, Marcocci C, Tanda ML, Manetti L, Dell'Unto E, Bartolomei MP, Nardi M, Martino E, Pinchera A** 1998 Cigarette smoking and treatment outcomes in Graves ophthalmopathy. Ann Intern Med 129:632–635
38. **Wiersinga WM, Bartalena L** 2002 Epidemiology and prevention of Graves' ophthalmopathy. Thyroid 12:855–860
39. **Bartalena L, Pinchera A, Marcocci C** 2000 Management of Graves' ophthalmopathy: reality and perspectives. Endocr Rev 21:168–199
40. **Gerding MN, Prummel MF, Wiersinga WM** 2000 Assessment of disease activity in Graves' ophthalmopathy by orbital ultrasonography and clinical parameters. Clin Endocrinol (Oxf) 52:641–646
41. **Gabriel M, Decristoforo C, Moncayo R** 2002 Somatostatin receptor scintigraphy using $^{99m}$Tc-EDDA/HYNIC-TOC in Graves' disease. Eur J Nucl Med Mol Imaging 29:1267
42. **Colao A, Lastoria S, Ferone D, Pivonello R, Macchia PE, Vassallo P, Bonavolonta G, Muto P, Lombardi G, Fenzi G** 1998 Orbital scintigraphy with [$^{111}$In-diethylenetriamine pentaacetic acid-D-phe1]-octreotide predicts the clinical response to corticosteroid therapy in patients with Graves' ophthalmopathy. J Clin Endocrinol Metab 83:3790–3794
43. **Loos U, Raptis S, Birk J, Escobar-Jimenez F, Meyer G, Rothenbuchner G, Pfeiffer EF** 1978 Inhibition of TSH-stimulated radioiodine turnover and release of T4 and T3 in vivo by somatostatin. Metabolism 27:1269–1273
44. **Bland JM, Altman DG** 1995 Multiple significance tests: the Bonferroni method. BMJ 310:170
45. **Kendall-Taylor, Dickinson AJ, Vaidya B, Miller M, Coulthard A, Perros P, Baster E, Andrews C, Hesse L, Heverhagen J, Heufelder AE** 2003 Double-blind placebo-controlled trial of octreotide LAR in thyroid-associated orbitopathy (TAO): clinical outcome. Thyroid 13:671 (Abstract)
46. **Bruns C, Lewis I, Briner U, Meno-Tetang G, Weckbecker G** 2002 SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. Eur J Endocrinol 146:707–716
47. **Prummel MF, Bakker A, Wiersinga WM, Baldeschi L, Mourits MP, Kendall-Taylor P, Perros P, Neoh C, Dickinson AJ, Lazarus JH, Lane CM, Heufelder AE, Kahaly GJ, Pitz S, Orgiazzi J, Hullo A, Pinchera A, Marcocci C, Sartini MS, Rocchi R, Nardi M, Krassas GE, Halkias A** 2003 Multi-center study on the characteristics and treatment strategies of patients with Graves' orbitopathy: the first European Group on Graves' Orbitopathy Experience. Eur J Endocrinol 148:491–495

**JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**