Slow-release lanreotide in Graves' ophthalmopathy: A double-blind randomized, placebo-controlled clinical trial

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ABSTRACT. SS analogs are an attractive alternative in treating Graves' ophthalmopathy (GO). Most of the previous studies were uncontrolled and enrolled few patients. The present study was conducted as a larger scale, prospective, randomized controlled study to determine the effectiveness of a slow-release formulation of lanreotide in GO. Sixty patients with active GO received an im injection every two weeks of either lanreotide 30 mg or placebo for 12 weeks. They were then followed and further treated in the traditional way if necessary. The Clinical Activity Score (CAS) was the primary efficacy criterion. Proptosis, diplopia, corneal erosion or ulcer, visual acuity, extraocular muscle movement and intraocular pressure were also evaluated. At the end of the 12 weeks, the mean CAS was not significantly decreased in the lanreotide group compared to the placebo group. The overall mean difference of proptosis between these two groups also did not reach significance at 12 weeks. Only diplopia at downward gaze had significant improvement for the lanreotide-treated group *vs* placebo group (p=0.03). No differences were observed between the two groups compared to other outcome measures. During the 24-month follow-up after the clinical trial, 14 patients received eye surgery in the placebo group compared with 10 patients in the lanreotide group (p=0.29). Six patients received methylprednisolone pulse therapy in the placebo group and two patients in the lanreotide group (p=0.25). In conclusion, lanreotide treatment had no significant effects on GO compared with placebo.

(J. Endocrinol. Invest. 29: 413-422, 2006)

INTRODUCTION

Graves' ophthalmopathy (GO), also called thyroid associated ophthalmopathy (TAO) or thyroid eye disease (TED), is an inflammatory process which usually occurs in patients with Graves' disease but can also be present in up to 10% of euthyroid subjects (1) or in patients having Hashimoto's thyroiditis (2).

This disorder is characterized by enlarged extraocular muscles and lymphocytic infiltration of retro orbital connective and fat tissues leading to specific clinical manifestations including proptosis, diplopia, eye pain, stinging and excess of tears. Proptosis can cause corneal damage. Edema and swelling of retro orbital tissues may lead to permanent visual loss from optic nerve compression.

Key-words: Lanreotide, somatostatin analogs, thyroid eye disease, thyroid associated ophthalmopathy, Graves' ophthalmopathy.

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Accepted January 13, 2006.

It is currently assumed that GO is an autoimmune disease developed as an immune response against antigen(s) shared by thyroid and orbit. The response of these antigens could be predominantly cell-mediated (3-5).

Activated T-lymphocytes infiltrate the orbital tissues and both lymphocytes and orbital fibroblasts produce several cytokines, including tumor necrosis factor-α, interferon-γ and growth factors such as IGF-I, which stimulate the synthesis of glycosaminoglycans (GAG), mainly the large, hydrophilic hyaluronic acid (6). Cytokine-stimulated fibroblasts also secrete various cytokines that might trigger further recruitment of activated lymphocytes and inflammatory cells, leading to further impairment within orbital tissue and a perpetuation of the orbital autoimmune reactions (5, 7).

Only the patients who are in the progressive stage of the disease need treatment. In 1992, we reported the therapeutic effectiveness of octreotide, a SS analog, in 6 patients with GO (8). The mechanism of action of SS analogs has not yet been fully clarified (9). These drugs may act by a direct inhibition of IGF-I mediated effects (10).

The justification for the use of SS analogs in GO came from the detection of binding sites for SS on retro orbital tissues of patients with GO as suggested by uptake of [^{111}In-diethylenetriamine pentaacetic acid-D-Phe^{1}]-octreotide into the orbit (11-13). Moreover, Pasquali et al. (14) demonstrated that orbital lymphocytes derived from retro orbital tissues of patients with GO expressed all subtypes 1-5 of functional SS-receptors (SSTR), while cultured fibroblasts specifically express SSTR 1-3 only, and adipose cells express SSTR 1-3 and SSTR 5 subtypes (15). These data suggest that SS analogs may modulate lymphocytes and orbital cell responsiveness as well as GAG production through their interaction with specific cell surface receptors (7).
The aim of the present study was to evaluate the therapeutic effect of a slow-release formulation of lanreotide, an SS analog, in patients with active GO.

MATERIALS AND METHODS

Study design

This was a single center, randomized, double-blind, parallel group and placebo-controlled trial performed at the National Taiwan University Hospital.

Patients

In all, 60 patients of Chinese origin with GO aged between 18 and 72 yr were enrolled. All had been informed of the study's conditions and had given their informed consent in writing before enrollment. They were screened for eligibility at the inclusion visit (day 0). Eligible patients had a clinically active GO with a clinical activity score (CAS) ≥3, at least in one eye. All patients had a treated thyroid disease with euthyroid state for at least 3 months and orbital computed tomography abnormalities were compatible with GO. The exclusion criteria were as follows: patients already treated with SS analogs, patients with known hypersensitivity to any of the test materials or related compounds, patients receiving systemic corticosteroids and/or treated by radiotherapy in the previous months, patients suffering from a known disease, likely to affect the ophthalmic evaluation, patients with a severe progressive disease, requiring heavy and protracted treatment, overt hepatic, renal or cardiac disease, patients with gallstone or gallbladder sludge, patients with diabetes mellitus, patients already taking part in another study, pregnant or breast feeding women, women of child bearing potential not using an effective contraceptive method during the study and 3 months following the withdrawal of the treatment.
Patients who fulfilled the inclusion criteria entered a 12-week treatment phase and accepted six injections during the trial, according to a 2-weekly dosage schedule.
The protocol of this clinical trial was approved by the Institutional Review Board of the National Taiwan University Hospital. The sponsor of the study was CentaPharm Inc.

Randomization: Treatment assignment

Treatment was administered only to those subjects included in this study, following the procedures set out in the clinical study protocol. The treatment cartons, whether they contained the active product or the placebo, were identical and randomized. Neither study staff nor examiners or participants were aware of the treatment allocation. The randomization schedule was generated in a defined block size 4 by Beaufour Ipsen International. Numbers from the randomization schedule were allocated in a strict sequence as patients were randomized at baseline (day 0). After the labelling of the study medication, the randomization code was stored under seal by the sponsor.

Study treatment

Study drug

Somatuline PR® is a microsphere-encapsulated slow-release formulation of lanreotide. It was provided by Beaufour Ipsen International as a powder in glass vials. Each vial was filled with a quantity of microparticles of lanreotide acetate and copolymers corresponding to 40 mg of lanreotide base, which ensured the actual injection of 30 mg of lanreotide.

Comparative medication

Matching placebo composed of microspheres of copolymere lactide-glycolide 265 mg; copolymere lactique-glycolique 5 mg; polysorbate 80, 2 mg; carboxymethylcellulose sodique 30 mg; mannitol 85 mg. Microspheres were suspended in the supplied solvent immediately before injection and the vial was shaken gently 20 to 30 times in order to obtain a homogeneous suspension with a milky aspect.

Treatment administration

Each eligible patient received 1 im injection of either lanreotide or placebo solution every two weeks (week 0, 2, 4, 6, 8 and 10) during the study period.

Study evaluations

Enrolled patients were examined at days 0 (baseline), 14, 28, 42, 56 and 84. The CAS was used to assess the disease activity (16). The CAS consisted of seven items and one point was given to each item present: pain with eye movement; spontaneous retro bulbar pain; eyelid erythema; eyelid edema or swelling; conjunctival injection; chemosis; caruncle swelling. In case of bilateral GO, the eye most affected was assessed.
The No physical sign or symptoms, Only signs, Soft-tissue involvement, Proptosis, Extraocular muscle involvement, Cornea involvement, Sight loss (NOSPECS) classification was used to assess the severity of the disease (17). This included the measurement of proptosis, as assessed by a Hertel exophthalmometer; diplopia, assessed at four directions and convergence, classified as 0=none, 0.5=mild diplopia, 1=remarkable diplopia. The corneal erosion or ulcer was evaluated as normal or abnormal by a slit lamp. If corneal erosion was present, the length, the width and the depth of the lesion were registered. The visual acuity was assessed by Snellen E Chart. The extraocular muscle movement was assessed at four directions (upward, downward, lateral gaze, medial gaze), classified as 0=none, 1=some restriction of motion, 2=limitation at extremes of gaze, 3=normal movement. The total score for each site was also calculated. The intraocular pressure was assessed with a tonometer and classified in three categories: <20 mmHg, between 20 and 30 mmHg and >30 mmHg.

Therapeutic outcome measures

The primary efficacy criterion was the mean change in total CAS from baseline (day 0) to the end of study treatment (day 84). Secondary outcomes were changes of proptosis, diplopia, corneal erosion or ulcer, visual acuity, extraocular muscle movement and intraocular pressure. Self-assessment of the eye conditions was evaluated by each patient on a scale (0=worse, 1=no change, 2=slight improvement, 3=significant improvement) at the end of study. The eye conditions include appearance, visual acuity, eye discomfort and diplopia. The total score was calculated.

Premature withdrawal

Subjects could withdraw from the trial at any time for any reason, without affecting their right to treatment by the investigator. The investigator had the right to withdraw a subject for any reason which was in the best interests of the subject, including concurrent illness, adverse events, or treatment failure.

Statistical analysis

The hypothesis of interest was that there was a treatment difference between treatment groups. Hypotheses were tested based on a two-sided test. A significance level of 0.05 was applied to the tests.

Descriptive statistics for patients' characteristics prior to randomization were obtained for each treatment group. Descriptive statistics of age, weight, height, and body mass index (BMI) and sex were tabulated. Only patients who received at least one injection and possessed at least one post-treatment efficacy assessment were included in the analysis of demography and baseline characteristics.

For continuous variables, the number, mean, SD, minimum, maximum and median were presented, and a t-test was applied to test the difference between the two treatment groups. For categorical variables, the numbers and percentages of subjects in each class were presented, and Fisher's exact test was performed.

The intent-to-treat (ITT) analysis was applied to the primary and secondary efficacy variables. All patients who received any amount of the study drug were included for the safety assessment. The method of last observation carried forward (LOCF) was used to account for premature withdrawals. Two non-parametric methods were used to analyse the primary efficacy criterion. A first quantitative approach based on the Mann-Whitney-Wilcoxon distribution free procedures (18) allowed us to obtain approximations of the *p*-value and the 95% confidence interval of treatment effect. A second non-parametric analysis compared between the treatment groups percentages of patients showing a decrease in the sum of CAS at the endpoint visit. This exploratory analysis seems to be relevant since CAS is a semi-quantitative variable defined by a little set of values. Sensitivity analysis took into account only patients who had an observed CAS performed at the final visit.

Other continuous outcome parameters were analyzed using the method of analysis of co-variance (ANCOVA model). Terms for treatment and baseline values were included in the statistical model. The qualitative variables were compared between treatment groups using Fisher's exact test. Additionally, the outcome parameters were analyzed using the mixed model with repeated measures, if applicable. This model includes random effect (drug effect based on randomized trial) and fixed effect (time effect).

Safety analysis

Adverse events were summarized according to Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). The number of patients who reported a particular event and the number of occurrence of the event were summarized. Comparative incidence of adverse events was evaluated using Fisher's exact test.

RESULTS

Characteristics of patients

A total of 60 patients were enrolled and 30 were randomized to the lanreotide group and 30 to the placebo group. Four patients withdrew from the study due to unsatisfactory therapeutic effect (lanreotide group: one; placebo group: three). One of three patients in the placebo group violated the protocol since his age was >70 yr old and withdrew from the trial after the first injection. Twenty-nine patients in the lanreotide group and 27 in the placebo group were considered to have completed all six injections.

Demographic characteristics and clinical features are summarized in Table 1 for the ITT population. There were no significant differences in demographic characteristics among the treatment groups. Lanreotide-treated patients had a longer mean duration of the disease than patients of the placebo group. However, the difference between the two groups was not statistically significant (p=0.24). Details regarding CAS and NOSPECS for each patient with GO in the lanreotide group and the placebo group are shown in Table 2.

There were 26 patients who received treatment with antithyroid drugs in the lanreotide group. One of them was also treated with radioactive iodine. There were 27 patients who received treatment with antithyroid drugs in the placebo group. Two of them were also treated with radioactive iodine.

Six patients in the lanreotide group and 6 in the placebo group had a smoking habit. There were no differences in the CAS between smokers and non-smokers either in the lanreotide (4.0±1.1, no.=12, *vs* 3.2±1.1, no.=48) or placebo group (3.8±1.2, no.=12, *vs* 3.2±0.9, no.=48). Eleven patients (36.7%) from each group had an optic nerve involvement. Their visual acuity could not be corrected by lens.

Effectiveness

Primary outcome

The mean changes of CAS from baseline are shown in Figure 1. At the end of the 2 week-treatment period, the mean CAS decreased by 0.67 in the lanreotide group compared to 0.20 in the placebo group. The treatment difference had a *p*-value of 0.05. At the end of the study, the difference between the two groups did not reach significance (treatment difference in the mean change of the CAS from baseline: 0.37; p=0.35).

Table 1 - *Demographics and characteristics of the patients with Graves' ophthalmopathy.*

	All treatment groups (no.=60)	Lanreotide (no.=30)	Placebo (no.=30)	Groups difference (*p*-value)
Age (yr)	43.0±11.2*	43.0±11.0	43.1±11.7	0.96
Sex no. (%) Female Male	 43 (71.7) 17 (28.3)	 19 (63.3) 11 (36.7)	 24 (80.0) 6 (20.0)	
Height (cm)	159.8±7.3	160.8±7.6	158.8±7.0	0.30
Weight (kg)	61.7±10.1	62.3±9.5	61.1±10.8	0.65
BMI (kg/m^2)	24.1±3.5	24.1±3.0	24.2±4.0	0.83
Graves' ophthalmopathy Duration (month) Median (range)	 15.3±16.9 9 (1-101)	 17.9±20.4 10 (3-101)	 12.7±12.2 9 (1-60)	0.24
Clinical activity score Median (range)	3.7±0.8 3 (3-6)	3.6±0.9 3 (3-6)	3.7±0.8 4 (3-6)	0.75
Proptosis (mm) Median (range)	19.9±2.4 20 (15-25)	19.8±2.3 20 (15-25)	19.9±2.4 20 (17-25)	0.87
Diplopia (total score of directions and convergence) Median (range)	4 1.6±1.8 1.0 (0-5)	1.5±1.6 1.0 (0-4.5)	1.7±1.9 1.0 (0-5)	0.74
Extraocular muscle movement (total score of 4 directions) Median (range)	9.5±1.9 10 (4-12)	9.5±2.3 10 (4-12)	9.6±1.5 10 (6-12)	0.79
Visual acuity (/10)	8.2±3.1	8.2±3.1	8.1±3.2	0.90
Slit lamp examination abnormal no. (%) normal	 27 (45.0) 33 (55.0)	 11 (36.7) 19 (63.3)	 16 (53.3) 14 (46.7)	0.30
Intraocular pressure <20 mmHg no. (%) Between 20 and 30 mmHg	 52 (86.7) 8 (13.3)	 27 (90.0) 3 (10.0)	 25 (83.3) 5 (16.7)	0.71

*Data are expressed as mean±SD. BMI: body mass index; N: number of patients.

The sensitivity analysis performed on the observed values of the change of the CAS between days 84 and 0 also showed the difference was not statistically significant between the two groups (p=0.90). Figure 2 displays the percentages of patients showing a variation of the CAS. No patient of the lanreotide group showed an increase in the sum of the CAS at the different visits compared with 5 patients of the placebo group. The percentages of patients showing an improvement (at least one point decrease) at day 14-, end point- and day 84-visits, respectively, are given in Figure 3.

Secondary outcomes

For the lanreotide-treated patients, mean proptosis values were significantly decreased 4 weeks after the first injection (p=0.03). At the end of treatment period, proptosis was reduced by 0.32 mm in the lanreotide group, while a smaller reduction (mean: –0.20 mm) was found among the patients receiving placebo. However, the difference was not significant (95% confidence interval –0.34 mm to 0.57 mm; p=0.61; Table 3, Fig. 4). Over the treatment period (using the repeated measures analysis with mixed model), the mean changes in proptosis value were –0.28 mm for the lanreotide-treated patients and –0.18 mm for placebo group. Patients treated with lanreotide had a statistically significant decrease in proptosis value (p=0.03), whereas a slight decrease was found among the patients treated with placebo (p=0.17). However, the overall mean difference between the two treatment groups did not reach significance (0.10 mm with 95% confidence interval –0.26 to 0.46 mm; p-value =0.57).

Diplopia evaluation

Table 4 summarizes the mean changes from baseline in diplopia and p-values. Patients treated with lanre-

Table 2 - *Details regarding clinical activity score (CAS) and No physical signs or symptoms, Only signs, Soft-tissue involvement, Proptosis, Extraocular muscle involvement, Cornea involvement, Sight loss (NOSPECS) for each patient with Graves' ophthalmopathy in lanreotide group and placebo group.*

	Lanreotide				Placebo			
	CAS		NOSPECS		CAS		NOSPECS	
	Right	Left	Right	Left	Right	Left	Right	Left
1	4	3	5a	5a	3	3	4a	5a
2	3	3	4a	4a	3	2	5a	4b
3	5	5	2c	5a	3	3	5a	5a
4	3	3	5a	5a	2	3	4b	5a
5	3	3	4c	4b	4	4	5a	5a
6	3	3	4a	4a	4	4	5a	5a
7	3	3	4b	5a	3	4	4a	4a
8	3	0	4c	0	4	4	6b	6b
9	4	4	4b	4b	2	3	2b	2b
10	3	3	3a	3a	4	2	6a	6c
11	3	2	6a	6b	6	5	6a	6a
12	4	4	3b	3a	4	2	5a	5a
13	5	5	5a	5a	4	3	5a	5a
14	3	3	4a	4a	3	3	4a	5a
15	3	3	4a	6a	3	3	4b	4b
16	4	4	6b	6b	3	3	2b	2b
17	6	6	6c	6b	4	5	6a	6a
18	3	3	4b	4b	3	1	5a	3b
19	1	3	2a	2b	4	3	4a	6a
20	3	3	4a	4a	3	2	5a	5a
21	3	2	6b	6a	5	5	6a	6a
22	4	0	6a	4a	4	5	6a	6b
23	2	3	6a	6a	3	3	5a	6a
24	3	1	2c	2a	3	3	6a	6a
25	4	4	6a	6a	2	4	4a	5a
26	4	4	6a	6a	4	4	6a	6a
27	3	3	5a	5a	4	2	6a	6a
28	5	3	6a	6a	3	1	6a	2a
29	4	4	4a	4a	3	2	3a	6a
30	5	5	6a	6a	4	4	4c	4c

otide had a statistically significant improvement on the diplopia only at downward gaze compared with placebo-treated patients (p=0.03).

There were no differences between the two groups compared to other outcome measures including corneal erosion/ulceration, visual acuity, extraocular muscle movement score and intraocular pressure (data not shown).

At the end of treatment, the most commonly reported NOSPECS class were extraocular muscle involvement (class 4, 40%) and sight loss (class 6, 33%) for lanreotide-treated patients, and sight loss

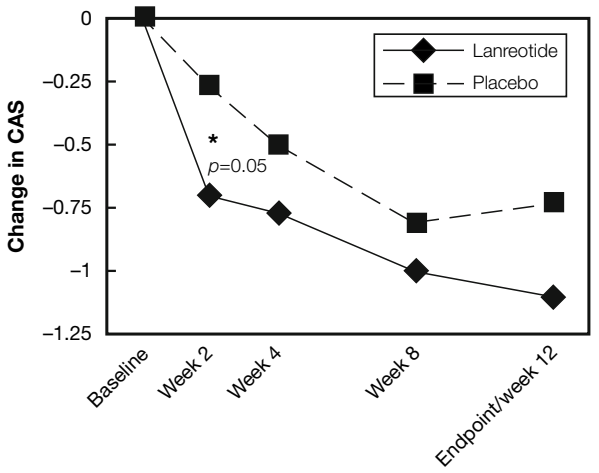

Fig. 1 - *Mean changes from baseline in the clinical activity score (CAS).*

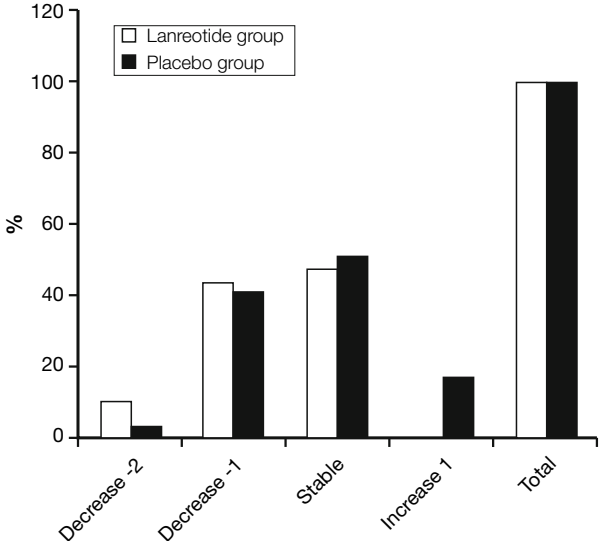

Fig. 2 - *Percentage of patients showing a variation of the clinical activity score.*

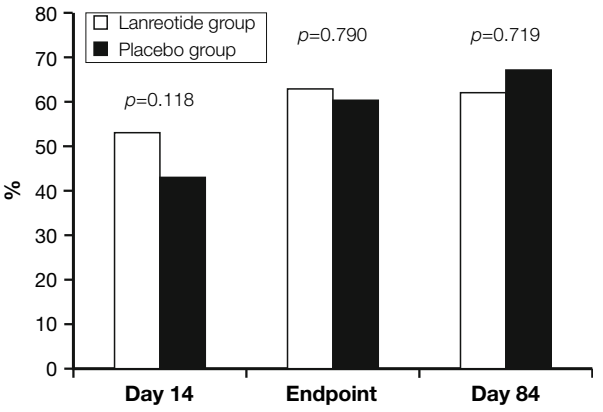

Fig. 3 - *Percentage of patients showing an improvement of the clinical activity score at day 14-, endpoint- and day 84-visits.*

Table 3 - *Comparison of the mean change from baseline in proptosis value (mm) between lanreotide group and placebo group (the mixed model least squares means).*

	Lanreotide	Placebo	Group difference *p*-value
Baseline No.	0 30	0 30	
Day 14 No.	–0.17±0.44 30	–0.10±0.82 30	0.70
Day 28 No.	–0.27±0.76** 30	–0.21±0.54 28	0.76
Day 56 No.	–0.38±0.78# 29	–0.35±0.73** 27	0.89
Day 84 No.	–0.34±0.79** 29	–0.35±0.69** 27	0.97
Endpoint analysis No.	–0.32±0.79* 30	–0.20±0.96 30	0.61

Data are expressed as mean±SD. #$p<0.01$ *vs* baseline; *$p=0.056$ *vs* baseline; **$p<0.05$ *vs* baseline.

(class 6, 36.7%) and extraocular muscle involvement (class 4, 26.7%) for the placebo group. Comparison of the difference in the NOSPECS classification between the two groups showed $p=0.58$ at baseline, and $p=0.14$ at end of treatment. Therefore, there was no statistically significant change at NOSPECS classification.

Self assessment total score

For patient's assessment, a higher mean score was observed in patients treated with lanreotide (5.8 *vs* 5.0 for placebo group). Despite a tendency toward improvement in eye condition among the lanreotide-treated patients, the results failed to reveal any statistically significant difference between the two groups ($p=0.22$; Table 5).

Safety

At least one treatment-emergent adverse event was experienced by all subjects in the lanreotide group compared with 70% of subjects in the placebo group. The commonly (ie, incidence >10%) reported adverse events in lanreotide-treated patients were diarrhea (86.7%), abdominal pain (50.0%), dizziness (23.3%), nausea (13.3%) and abdominal distension

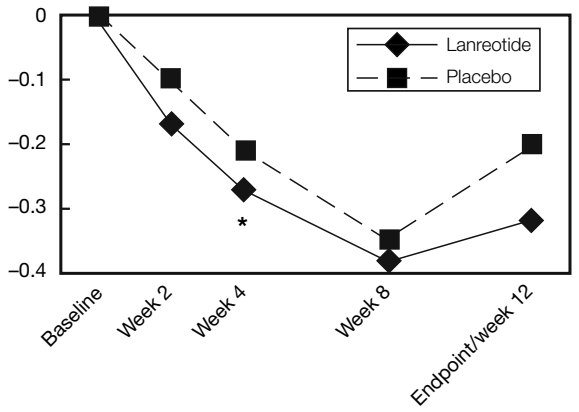

Fig. 4 - *Mean changes from baseline in proptosis value (mm). *p=0.03 vs baseline.*

(13.3%). For placebo-treated patients, the commonly reported adverse event was diarrhea (36.7%). Incidence of diarrhea and abdominal pain was statistically significant between treatment groups ($p<0.0001$). Overall, the majority of treatment-emergent adverse events reported during the study were mild in severity.

During the 24 months follow-up after the clinical trial, 14 patients received eye surgery in the placebo group compared with 10 patients in the lanreotide group ($p=0.29$), and 6 patients received methylprednisolone pulse therapy in the placebo group compared with two patients in the lanreotide group ($p=0.25$).

DISCUSSION

The primary objective of this randomized, placebo-controlled, single center trial was to evaluate the clinical effectiveness and safety of lanreotide 30 mg in patients with GO. The primary response criterion was the reduction of the CAS. Due both to the analysis of decrease of CAS and the analysis of improvement, the results did not show a statistical difference between the two treatment groups. However, it is noteworthy that no patient receiving lanreotide showed an increase in the sum of disease activity score at the different visits compared to 5 patients (16.7%) in the placebo group. The study drug significantly reduced the proptosis but the decreases of scores at the end of the treatment were not statistically different between the two groups. The main beneficial effect of the treatment was observed during diplopia evaluation, but only on the diplopia at downward gaze compared with placebo-treated patients.

Lanreotide is a long-acting SS analog depot which was developed to eliminate the necessity of multiple daily injections of the previous SS analogs and, thus, improve patients' compliance. There is so far only one published placebo-controlled study on the efficacy of this compound in GO (19, 20). Taking into account that a correlation exists

Table 4 - *Summary of the mean changes from baseline in diplopia evaluation.*

		Lanreotide	Placebo	Treatment difference	*p*-value
Upward gaze	Baseline	0.5±0.48	0.4±0.49	–0.1±0.48	0.51
	Day 84	0.3±0.45	0.4±0.47	0.0±0.46	0.73
	Change from baseline	–0.10±0.39	0.00±0.31	0.10±0.35	0.33
Downward gaze	Baseline	0.3±0.43	0.3±0.46	0.0±0.45	0.77
	Day 84	0.2±0.36	0.4±0.49	0.2±0.43	0.06
	Change from baseline	–0.12±0.35	0.06±0.35	0.18±0.35	0.03
Right side gaze	Baseline	0.4±0.46	0.4±0.48	0.0±0.47	1.00
	Day 84	0.1±0.35	0.3±0.44	0.2±0.40	0.14
	Change from baseline	–0.19±0.36	–0.06±0.42	0.13±0.39	0.10
Left side gaze	Baseline	0.3±0.43	0.4±0.50	0.1±0.47	0.27
	Day 84	0.2±0.39	0.4±0.50	0.2±0.45	0.10
	Change from baseline	–0.07±0.35	0.00±0.39	0.07±0.37	0.20
Convergence	Baseline	0.2±0.36	0.3±0.43	0.1±0.40	0.52
	Day 84	0.1±0.28	0.2±0.40	0.1±0.34	0.14
	Change from baseline	–0.09±0.23	0.00±0.24	0.09±0.24	0.07

The data are expressed as Mean±SD. The diplopia is classified as 0= none, 0.5= mild diplopia, 1= remarkable diplopia.

Table 5 - *Summary of final self-assessment.*

	Lanreotide No. (%)	Placebo No. (%)	Treatment difference *p*-value
Appearance			0.76
Worse	3 (10.0)	5 (16.7)	
No change	7 (23.3)	8 (26.7)	
Slight improvement	16 (53.3)	15 (50.0)	
Significant improvement	4 (13.3)	2 (6.7)	
Visual acuity			0.90
Worse	8 (26.7)	10 (33.3)	
No change	16 (53.3)	16 (53.3)	
Slight improvement	4 (13.3)	3 (10.0)	
Significant improvement	2 (6.7)	1 (3.3)	
Eye discomfort			0.87
Worse	3 (10.0)	5 (16.7)	
No change	7 (23.3)	7 (23.3)	
Slight improvement	11 (36.7)	11 (36.7)	
Significant improvement	9 (30.0)	7 (23.3)	
Diplopia			0.77
Worse	3 (10.0)	5 (16.7)	
No change	20 (66.7)	20 (66.7)	
Slight improvement	4 (13.3)	4 (13.3)	
Significant improvement	3 (10.0)	1 (3.3)	
Total score	5.8±2.5	5.0±2.5	0.22

Score 0= worse, 1= no change, 2= slight improvement, 3= significant improvement.

between the efficacy of the drug and the presence of SSTR in the orbital tissues as detected by orbital uptake of ^{111}In-DTPA-D-Phe^{1}-octreotide (octreoscan-111) (13, 21-23), Krassas et al. (19) studied 5 patients selected on the basis of positive orbital scintigraphy. The trial demonstrated the beneficial effect of lanreotide in these patients having severe symptoms of GO. Moreover, it showed that orbital uptake disappeared completely in all patients after treatment (20). These results agree with those of several published studies conducted with the immediate release formulation of octreotide (8, 9, 12, 24). However in Kung's study, neither octreotide nor glucorticosteroids significantly improved proptosis measured by magnetic resonance imaging (MRI), while urinary GAG levels decreased substantially after both treatments (25).

Our results do not consolidate those of Krassas. However, they are in line with those of a more recent placebo-controlled trial conducted by Wemeau et al. (26). Fifty-one patients were treated with a long-acting formulation of octreotide (octreotide-LAR) over a 16-week period. Although the CAS score was reduced in the octretide-LAR group, there was no significant difference with the placebo group. Proptosis was significantly reduced, but non-significant differences were observed in several proptosis-related parameters. There were no statistically significant changes in self-assessment. Dickinson et al. (27) did not find any therapeutic effect of octreotide-LAR in the double-blind placebo-controlled trial they conducted in 50 euthyroid subjects with moderately severe, active GO.

In our study, the lack of initial response to treatment could be firstly related to the patients' selection, which was built on the sole 7-point CAS as determined during a single visit. Thus, our patients' sample may not have adequately covered those who will be good responders (28). Some authors (29, 30) stated that CAS evaluation usually fails to assess whether or not the disease is still in the early stage of inflammation, when immunotherapy is beneficial. According to Mourits et al. (31, 32), the higher the CAS, the better the treatment outcome. As the mean value of CAS in our population was <4, the poor responsiveness to lanreotide of our patients could be due to the fact that most of them were at a poorly active stage of a long-standing disease. Secondly, our definition of success of treatment is probably in part inaccurate. The lack of objective and quantitative measurements could count against an adequate appraisal of the effectiveness of treatment (33). We found previously that, although the activity score seems to be a predictor of initial responsiveness to anti-inflammatory drugs, it does not

guarantee the final results of the treatment (34). Additional disease markers have been suggested in order to improve the sensitivity of the CAS (35-37). Gorman et al. (38) and Frueh (39) considered that it is best to use measurable attributes such as range of extraocular muscle motion, area of diplopia fields, volume of extraocular muscle and fat, lid fissure width and proptosis. Chen et al. (40) proposed calculation of the width from the largest portion of the muscle manually to assess the severity of extraocular muscle involvement, and we suggested that good responders had minimal enlargement of extraocular muscles (34). Some authors stated that MRI could be effective in selecting patients who need immunosuppressive therapy (36, 41). Other researchers claimed that a scintigraphy with labelled octreotide is more appropriate as it reveals activated cells within the orbit and also predicts the response to the treatment (22). However, the published results as regards to the predictive value of orbital scintigraphy are somewhat conflicting. Durak et al. (42) did not observe any correlation between baseline scan and treatment efficacy and 3 out of 5 positive patients did not respond to octreotide therapy. Wemeau et al. (26) failed to detect any significant relationship between baseline SSTR-scan and the treatment outcome. In addition, this technique is highly expensive. Gerding et al. (30) suggested adding A-mode ultrasonography (a cheap, non-invasive and safe technique) to the CAS and the disease duration, whereas Doumas et al. (43) proposed imaging with ^{99m}Tc-depreotide as an alternative to SSTR-scintigraphy. Preliminary results seem to be encouraging.

In our study, we performed neither SSTR-scan nor ultrasound evaluation before inclusion. Although orbital computed tomography (CT) imaging of the orbit was used for diagnosis, our objective was not to assess the predictive value of the tomographic parameters (34).

Finally, lanreotide binds much better to SSTR 2 than to other subtypes. It is known to be a highly potent suppressor of human GH (hGH) secretion in active acromegaly. However, some acromegalic patients are resistant to SS analogs. As qualitative or quantitative differences in the expression of SSTR on connective tissue exist, perhaps we ought to have adjusted dosing of the drug during the study period according to patients' responsiveness.

In conclusion, lanreotide had no significant effects on patients with GO compared with placebo in our study. It should not be employed for GO in the clinical practice, also in view of the very high costs of treatment.

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