NOTE

Effect of Octreotide Treatment on Graves' Ophthalmopathy

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Abstract. In this study, nine patients with Graves' ophthalmopathy with positive clinical activity score (CAS), who were either unresponsive or not suitable for glucocorticoid treatment, were given 100 µg of octreotide three times daily, subcutaneously, for three months. The mean age was 49 ± 13 years. All patients were under either propylthiouracil or methimazole therapy and were euthyroid for at least one month prior to the start of the octreotide treatment. The mean degree of proptosis as measured with the Hertel exophthalmometer decreased slightly after the treatment (22.0 ± 3.0 vs 19.6 ± 2.4 for the right eye and 22.2 ± 1.9 vs 20.2 ± 2.2 for the left eye; $p < 0.05$). The mean activity score decreased from 3.2 ± 0.8 to 1.7 ± 1.1 ($p < 0.005$) and the mean score of eye signs according to the NOSPECS classification showed improvement with octreotide therapy (3.2 ± 0.7 vs. 2.2 ± 1.4 ; $p < 0.05$). Seven patients responded favorably to octreotide treatment. In the remaining two no improvement was observed. Four of the responders could be followed up for 20 months after the treatment and all maintained the favorable state of eye findings obtained with octreotide. We conclude that octreotide seems to be a safe and effective drug in Graves' ophthalmopathy, especially in improving soft tissue involvement, and can be used in patients who are unresponsive to glucocorticoid treatment or who cannot use these drugs for some reason.

Key words: Graves' ophthalmopathy, Octreotide

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GRAVES' ophthalmopathy (GO) is an autoimmune disease that affects orbital tissue and in its severe forms may compromise vision. Different treatment methods, such as immunosuppressive treatment, orbital irradiation and decompression (surgery), have been used for the treatment of moderate to severe GO [1–3]. These existing treatments are not fully satisfactory and have several major and/or minor side effects. Octreotide (OCT), a potent somatostatin analogue which has been used for the treatment of several diseases, has recently been proposed as an effective drug in the treatment of GO in some studies [1–5], but there is doubt about its value since it was found to be not beneficial in one study [6].

The purpose of this study is to assess the efficacy of OCT on the disease activity, estimated by clinical activity scoring (CAS), in patients with moderately severe GO who cannot tolerate or are unresponsive to corticosteroid (CS) therapy.

Patients and Methods

Patients

Nine patients (4 males, 5 females, mean age 49 ± 13 years) with active GO were included in the study. The duration of Graves' ophthalmopathy was 3–36 months (mean 14.2 ± 11.3) and none was a smoker. All the patients were euthyroid for at least one month on antithyroid drugs (propylthiouracil or methimazole) before the start of the study. Three patients had received radioiodine therapy for hyperthyroidism two years before. Five patients had received 1–1.5 mg/kg/day corticosteroid (CS) ther-

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apy for approximately six months for GO previously but no improvement occurred and had been off CS for at least three months (mean 4.33 ± 1.53 months) prior to the study. The remaining four patients were not appropriate candidates for CS therapy since they had either active gastritis or peptic ulcers on endoscopy. One patient had had an eye muscle operation for strabismus.

Methods

Octreotide acetate (OCT) (Sandostatin, Sandoz Pharma Ltd) 100 μ g, subcutaneously, three times a day, was given to the patients. The total study period was three months. The euthyroid state was maintained and the patients received no other treatment for GO during the study. The study was approved by the local Ethical Committee and informed consent was obtained from all the patients.

Assessment of Efficacy

Eye Scoring: All patients were evaluated by the same physician (D.Ç.) once every two weeks during the study. Proptosis was measured with a Hertel exophthalmometer. Limits for proptosis were adjusted for the local population [7]. NOSPECS classification was recorded as, Class 0, No physical signs

or symptoms; Class I, Only signs, no symptoms; Class II, Soft tissue involvement; Class III, proptosis; Class IV, extraocular muscle involvement; Class V, corneal involvement; Class VI, optic nerve involvement. Disease activity was assessed by assigning 1 point for the presence of each of the following signs and symptoms: spontaneous retrobulbar pain, pain on eye movement, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle and eyelid edema or fullness and the sum of these points was the clinical activity score (CAS; range 0–7) [8]. Moderately severe ophthalmopathy was defined as being in one of the following NOSPECS categories: either Class II with severe soft tissue involvement or Class III or IV. Two millimeters or more decrease in the proptosis value and one or more point decrease in the activity score were accepted as improvement.

Orbital computerized tomography or magnetic resonance imaging (MRI) scans were carried out on patients before the treatment and all showed some degree of involvement in extraocular muscles which was determined by muscle size measurements.

Statistics: All statistical analyses were performed by Wilcoxon matched pairs' tests. For correlation analysis Kendall's tau-b test was used. A P values less than 0.05 was regarded as significant.

Table 1. Clinical characteristics of the patients before octreotide treatment.

Case Number	Age (Year)	Sex	Disease Duration (months)	NOSPECS# Classification (Class)	Clinical Activity Score* (CAS)	Prior Medical Therapy
1	37	F	6	III	4	CS
2	47	M	3	II	4	(–)
3	50	F	24	III	2	CS, RAI
4	49	M	10	III	4	(–)
5	33	F	7	III	2	(–)
6	63	M	12	IV	4	CS, RAI
7	37	M	24	III	3	CS
8	74	F	36	IV	3	RAI, Op.
9	52	F	6	IV	3	CS

CS: Corticosteroid, RAI: Radioiodine treatment, Op: Operation for strabismus, #NOSPECS Classification: Class 0; No physical signs or symptoms, Class I; Only signs, no symptoms, Class II; Soft tissue involvement, Class III; Proptosis, Class IV; Extraocular muscle involvement, Class V; Corneal involvement, Class VI; Optic nerve involvement, *CAS: Spontaneous retrobulbar pain, pain on eye movement, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle and eyelid edema or fullness; and the sum of these points was the clinical activity score (range 0–7).

Results

Extraocular muscle involvement, evaluated as enlargement of the muscles, was observed in all patients either by CT or MRI: enlargements affecting the in-

ferior, medial and superior rectus muscles in three cases (cases 6, 8, 9) and enlargements affecting one or two rectus muscles in the remaining six.

The clinical characteristics of the patients are shown in Table 1. The mean CAS decreased significantly from 3.2 ± 0.8 to 1.7 ± 1.1 after treat-

Table 2. Activity scores and proptosis measurements of patients before and after octreotide treatment.

Patient Number	Clinic Activity Score (CAS)		Proptosis (mm)		
		Before	After	Before	After
1	Eyelid edema	+	—	Right Eye	22
	SRP	+	—	Left Eye	21
	PEM	+	+		20
	Eyelid Erythema	+	+		19
	Score	4	2		
2	Eyelid Edema	+	—	Right Eye	19
	SRP	+	+	Left Eye	22
	Eyelid Erythema	+	—		20
	Caruncle Swelling	+	—		
	Score	4	1		
3	Eyelid Edema	+	—	Right Eye	26
	Caruncle Swelling	+	+	Left Eye	24
	Score	2	1		25
4	Eyelid Edema	+	—	Right Eye	24
	Caruncle Swelling	+	—	Left Eye	24
	SRP	+	+		19
	Eyelid Erythema	+	—		19
	Score	4	1		
5	Eyelid Edema	+	+	Right Eye	23
	PEM	+	—	Left Eye	24
	Score	2	1		21
6	Eyelid Edema	+	+	Right Eye	23
	SRP	+	+	Left Eye	24
	PEM	+	+		21
	Conjunctival Injection	+	+		22
	Score	4	4		
7	Eyelid Edema	+	+	Right Eye	24
	Eyelid Erythema	+	—	Left Eye	22
	Conjunctival Injection	+	—		19
	Score	3	1		
8	Eyelid Edema	+	+	Right Eye	16
	SRP	+	+	Left Eye	19
	Eyelid Erythema	+	+		16
	Score	3	3		19
9	Eyelid Edema	+	—	Right Eye	21
	Eyelid Erythema	+	+	Left Eye	20
	Conjunctival Injection	+	—		17
	Score	3	1		17
Mean $\pm$ SD		3.2 ± 0.8	$1.7 \pm 1.1^*$	22 ± 2.4	$20 \pm 2.5^{**}$

SRP: Spontaneous retrobulber pain, PEM: Pain on eye movement, * $p < 0.005$, ** $p < 0.05$

ment ($p < 0.005$). The mean degree of proptosis, as measured with the Hertel exophthalmometer, also decreased slightly after the treatment (22 ± 2.4 vs 20 ± 2.5 in total, 22.0 ± 3.0 vs 19.6 ± 2.4 for the right eyes and 22.1 ± 2.0 vs 20.3 ± 2.6 for the left eyes; $p < 0.05$). (Table 2). The NOSPECS score also showed improvement with the treatment (3.2 ± 0.7 vs. 2.2 ± 1.4 ; $p < 0.02$).

When evaluated individually seven of the patients showed improvement in their activity scores with octreotide. Proptosis improved either slightly or significantly in 7 patients and three of these had normal proptosis values at the end of the study (case 4, 7, 9). Proptosis values did not change in one patient (case 8) and slightly decreased but still remained in high values in one patient (case 3). Two of the three patients (cases 6, 8 and 9) who were complaining of diplopia showed improvement at the end of the study (cases 6 and 9). Two patients (cases 6 and 8) showed no improvement in activity scores but in one of these patients proptosis decreased with OCT (case 6). No patient showed deterioration in the eye findings.

No difference in the therapeutic effects could be found between CS- unresponsive and CS- unsuitable patients ($p > 0.05$ for both the activity score and proptosis value).

Four patients, who could be followed up after OCT treatment, remained favorable condition during the 20 month follow up. The other three responders did not come for their control visits after the third month since they wanted to be followed up by their local physician (Cases 1, 4, 9).

Three patients complained of abdominal pain and diarrhea and all had flatulence caused by the therapy. The adverse effects were eliminated in the second week of the treatment.

Discussion

These data confirm that OCT is effective in improving proptosis, diplopia and soft tissue involvement in patients with GO. The drug was beneficial

in reducing both CAS and NOSPECS scores. The clinical activity score, one of the methods used to estimate disease activity, ameliorated in seven of nine, and the mean proptosis value decreased in seven and even normalized in three patients in a local population. Although it is hard to draw a conclusion from such a small number of patients, disease duration seemed to be a predictor of response to OCT, namely related to the disease activity, since five of the responders in the present study had a disease duration of less than 12 months.

In a number of recent studies OCT was found to be beneficial in GO [1–5, 9]. Özata *et al.* [1] found the drug to be effective in 8 of 10, Chang *et al.* [2] in 5 of 6, Kung *et al.* [4] in 8 of 8, Khoo *et al.* [5] in 6 of 8, and Krassas *et al.* [9] in all of 12 patients. Recently it was suggested that only octreotide orbital scanning (OctreoScan) positive patients benefit from this therapy [3, 9, 10]. On the other hand Durak *et al.*, who used OCT in three OctreoScan positive patients, found no beneficial effect of the drug [6]. We did not perform OctreoScan in our patients, as it is expensive and time consuming. In addition a positive correlation between disease activity and OctreoScan - 111 uptake was reported by some investigators and it is well known that the clinical activity test is very cheap and easy to perform [11, 12].

The exact mechanism of OCT in GO has not yet been determined clearly. It was shown that OCT decreased urinary GAG [13]. Moreover, it was reported that somatostatin treatment could decrease the plasma concentration of IGF - 1 [5, 13, 14] and could directly inhibit the release of lymphokines from lymphocytes [3, 9].

In conclusion, OCT seems to be safe and effective in the treatment of GO. The disadvantages of this treatment method are its expense and that because it has to be given three times as injections, patient selection becomes important. OCT can be used in patients who are unresponsive to CS therapy and/or in whom CS is contraindicated, but the number of patients treated with octreotide was small, and further studies are needed to confirm the results.

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