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Hormonal Secretion and Quality Of Life in Nelson Syndrome and Cushing Disease After Long Acting Repeatable Octreotide: A Short Series and Update

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Clinical management of persistent adrenocorticotropin hormone (ACTH) excess in Nelson syndrome (NS) and Cushing disease (CD) remains a challenge. Somatostatin and its analogs as octreotide decrease ACTH secretion through somatostatin receptors of pituitary cells. To our knowledge, there are no reports on the effect of long-acting repeatable octreotide (oct-lar) on hormonal secretion and quality of life in patients with NS and CD who failed conventional therapy. Herein, we describe the effects of treatment with oct-lar (20 mg/month intramurally) in 1 woman with NS and 2 women with persistent CD. Oct-lar therapy reduced ACTH secretion and improved the quality of life in NS patient. By contrast, in CD patients, it failed to control ACTH and cortisol secretion, and the quality of life remained unchanged.

Keywords: Nelson syndrome, Cushing disease, octreotide-LAR, quality of life

INTRODUCTION

Medical therapy for the management of Nelson syndrome (NS) and persistent Cushing disease (CD) remains a challenge. Many drugs with neuromodulatory properties (dopamine agonists, somatostatin and its analogs, gamma-aminobutyric acid agonists, serotonine antagonists, thiazolidinediones, and retinoic acid) and drugs that affect glucocorticoid synthesis or function (aminoglutethimide, metyrapone, ketoconazole, etomidate, mitotane, trilostane, mifepristone) have been tried to control NS and CD.[1,2]

Somatostatin (SS), considered a physiological regulator of growth hormone inhibits in vitro growth hormone secretion as well as inhibits prolactin, thyroid-stimulating hormone, and adrenocorticotropin hormone (ACTH) by rat anterior pituitary cells.[3] SS exerts its activity through SS receptors (sst). There are 7 transmembrane receptors coupled to G proteins and 5 subtypes have been identified (sst_1, sst_2, sst_3, sst_4, and sst_5).[4] In normal rat corticotropins, all 5 sst colocalize with ACTH-expressing cells.[5] Studies in vitro demonstrated a predominant expression of sst_5 messenger RNA in human corticotropic adenomas, although the majority of adenomas express sst_2 as well.[3]

Based on the structural and pharmacological characteristics, 2 subclasses of SS analogs (SSA) have been developed: octreotide and lanreotide that bind to sst_2, sst_3, and sst_5 and pasireotide that binds with higher affinity to sst_5,[6] the latter being a more potent inhibitor of ACTH secretion in primary cultures of human corticotropic adenomas than octreotide.[7] Despite its properties, pasireotide is not still available for clinical use.

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Subcutaneously delivered octreotide has been proposed as an adjuvant therapy in NS, CD, and ectopic Cushing syndrome (CS), with variable responses,[8–16] but this therapy requires multiple daily subcutaneous injections, rendering it unaffordable. Fortunately, a depot formulation as long-acting repeatable octreotide (oct-lar) is available for clinical use, although to our knowledge, there is no enough experience with this compound on hormonal control and quality of life in patients with NS and CD.

The short-form 36 (SF-36) health survey, an integrated measure of physical and psychological well-being, has been described as an useful tool for the assessment of quality of life in CS.[17] This study aims to show the effect of monthly administered oct-lar on ACTH levels, cortisol excretion, signs of tumor growth, and quality of life in 1 woman with NS and 2 women with persistent CD.

SUBJECTS AND METHODS

Patients

Case 1

This 59-year-old woman was referred for follow-up of NS. She had developed CS at the age of 15, surgically treated with total bilateral adrenalectomy and on steroid replacement therapy. Four years later, her skin darkened and complained of frontotemporal headaches (left sided) and reduced left visual acuity. An x-ray showed a wide sella turcica. She received external pituitary radiotherapy, and 6 months later, she had transcranial pituitary surgery. She had bacterial meningitis, which responded initially well to antibiotics but with severe recurrences. Finally, an enlarged and erosive sella turcica was identified on the x-ray films. A new series of cobalt therapy was followed by total hypophysectomy through craniotomy, but 6 months later, a second craniotomy was performed to close a fistula and excise residual tumor. The pathology demonstrated a recurrent pituitary adenoma, predominantly basophilic. However, the patient remained hyperpigmented, with impaired smell function and atrophy of both optic disks but without significant reduction in visual acuity. There was a definite bitemporal field defect in the upper quadrant.

Skin pigmentation increased along time, although x-ray films did not show tumor growth, but ACTH reached values of 792.0 pM. At that time, cyproheptadine was administered with significant reduction in ACTH levels to 308.0 pM, although changes in tumor size could not be identified. Despite the reduction in ACTH levels, she gained 30 kg of weight, and cyproheptadine was discontinued.

Fifteen years later, magnetic resonance imaging (MRI) of the sella showed tumoral invasion of the left cavernous sinus and medial displacement of the third cranial nerve. As tumor progressed, a fourth transcranial pituitary surgery was performed with postoperative cobalt therapy.

At the time of referral, ACTH levels were 278.0 pM, skin was dark, and she had left eye blindness and palsy of the third cranial nerve. Her memory was impaired, had insomnia, poor concentration, emotional lability, and complained of tiredness and apathy. She was on 30 mg of hydrocortisone, 0.1 mg of fludrocortisone, 100 μg of LT4, and 800 mg of carbamazepine every day. Sellar MRI had not changed since the last pituitary surgery. To control ACTH secretion and tumor growth through the modulation of sst receptors, oct-lar was prescribed at monthly doses of 20 mg intramurally. Quality of life was evaluated before and after the medical treatment.

Case 2

This 49-year-old woman had remission of CD after selective resection of an ACTH-pituitary microadenoma. Five years later, she started with fatigue, muscle weakness, loss of memory, emotional lability, plethora, increased body weight, and high blood pressure. Biochemical recurrence of CS was confirmed. Sellar MRI did not show any abnormality but inferior petrosal sinus sampling localized a pituitary ACTH source. She underwent total hypophysectomy, and pituitary histology revealed an area of microhyperplasia that positively stained for ACTH. After total pituitary resection, the patient persisted with active CS. Patient refused cobalt therapy and started on ketoconazole, developing toxicity to this drug. She tried on aminoglutethimide achieving well control of cortisol excess, but the drug became unavailable in our country. Oct-lar was prescribed at monthly doses of 20 mg intramurally for a period of 4 months.

Case 3

This 53-year-old woman was referred with diagnosis of CD and moderate signs and symptoms of cortisol excess. She had negative pituitary MRI, but positive pituitary ACTH gradient through inferior petrosal sinus sampling and underwent total hypophysectomy. Pituitary histology did not show evidence of corticotropic hyperplasia, but the presence of Crooke changes. She persisted with cortisol excess, and gamma-knife radiosurgery was indicated. While waiting for the effect of radiosurgery and due to severity of physical

and emotional status, she started on ketoconazole that was discontinued for hepatic toxicity. Oct-lar was initiated at monthly doses of 20 mg intramurally for as long as 4 months.

Methods

Plasma and 24-hour urine samples were obtained in 3 nonconsecutive days within the same week. Total urinary free cortisol (UFC) was determined by radioimmunoassay using coat-a-count kit after the extraction of 500 μL of urine with 1 mL of dichloromethane, as described by the manufacturer (Diagnostic Products Corporation), the minimal detectable dose was 6.0 nM. The intraassay and interassay coefficients of variation were <7.0% and 8.0%, respectively. The accuracy of 24-hour urine collection was confirmed by measuring creatinine excretion. Plasma ACTH was measured by IRMA (Diagnostic Systems Laboratories, Webster, TX). The minimum detection limit was 0.286 pM. Intraassay and interassay coefficients of variation were <9.4% and 8.0%, respectively.

Quality of life was assessed before and after octreotide therapy through SF-36, which is an integrated measure of the physical and psychological well-being. The SF-36 is a generic service that has been widely validated and used in an international context to evaluate self-reported domains of health status. It consists of a 36 item questionnaire that includes 8 components: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional health, and mental health.

Fifty age-matched healthy women constituted the control group to establish the appropriate age–gender norm. Scores were calculated as the sum of (recoded) scale items and transformed to a 0 to 100 scale according to the formula: Raw score − minimum possible raw score × 100/possible raw score range, as described.[18,19]

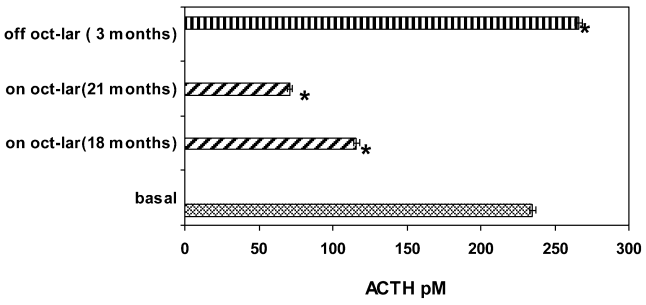

FIGURE 1. ACTH levels in a patient with NS (case 1) before and after 18 and 21 months on oct-lar and 3 months off this drug. *Basal versus on oct-lar (18 and 21 months) and off oct-lar (3 months) ($P < 0.0001$).

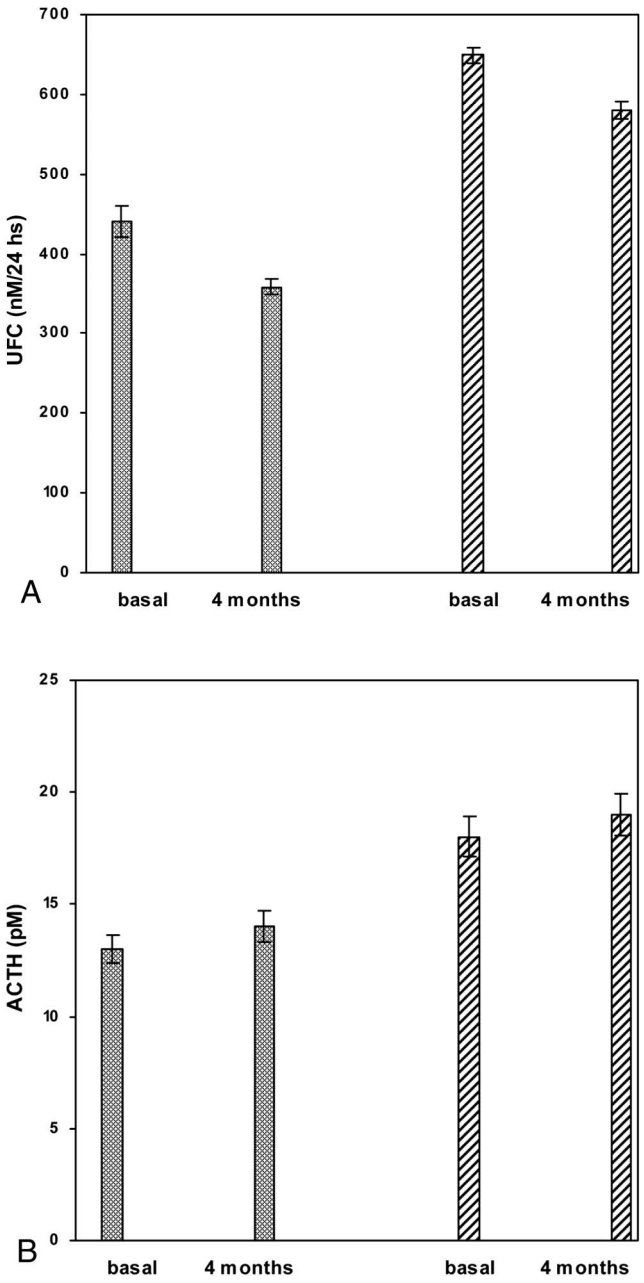

FIGURE 2. A, Levels of UFC in 2 patients with CD (cases 2 and 3) before and after 4 months on oct-lar. B, Levels of ACTH in 2 patients with CD (cases 2 and 3) on before and after 4 months on oct-lar.

Statistics

Data are expressed as mean ± SD from 3 nonconsecutive samples. The differences between hormone levels before and after the treatment were compared by analysis of variance, using the Statistical Package for the Social Sciences (SPSS, IBM Corporation, Armonk, NY). P values <0.05 were considered statistically significant.

Table 1. SF-36 scale scores from 3 patients in basal conditions and after oct-lar treatment for each component.

	Domain scores SF-36*							
	PF	RP	BP	GH	VT	SF	RE	MH
Patient 1								
Basal	35.0	25.0	32.0	25.0	10.0	25.0	33.3	56.0
On oct-lar (18 mo)	40.0	25.0	42.0	45.0	35.0	50.0	66.6	76.0
On oct-lar (21 mo)	60.0	50.0	58.0	57.0	65.0	87.5	66.6	88.0
Off oct-lar	55.0	50.0	42.0	57.0	55.0	62.5	33.3	80.0
Patient 2								
Basal	5.0	25.0	32.0	25.0	5.0	25.0	33.3	32.0
On oct -lar (4 mo)	15.0	25.0	42.0	15.0	25.0	25.0	33.3	24.0
Patient 3								
Basal	40.0	25.0	42.0	45.0	5.0	37.5	33.3	48.0
On oct-lar (4 mo)	55.0	25.0	50.0	47.0	10.0	37.5	33.3	32.0
C								
Mean ± SD	86.0 ± 12.0	91.0 ± 17.0	81.0 ± 12.6	71.0 ± 12.7	64.4 ± 16.5	83.9 ± 16.4	50.0 ± 15.0	70.0 ± 14.0
Threshold†	≥60.0	≥50.0	≥58.0	≥57.0	≥45.0	≥52.0	≥66.0	≥52.0

*Scores: see Methods.

†Higher scores represent better health-related quality of life, and the threshold is the minimum score associated to this condition.

C, age-matched healthy women (n = 50); BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.

Table 2. Literature update on subcutaneous octreotide in NS.

Author	Patients, n	Medical therapy	Results
Lamberts et al[8]	1	Octreotide (SMS 201-995) 300 μg/day subcutaneously for 2 years	ACTH ↓ No changes in tumor size
Petrini et al[9]	1	Octreotide (SMS 201-995) 300 μg/day subcutaneously for 2 years	ACTH ↓ Tumor size reduction 10%
Kelestimur et al[10]	1	Octreotide (SMS 201-995) 300 μg/day subcutaneously for 7 days	ACTH ↓ Tumor size reduction 3 mm
Kemink et al[11]	2	Octreotide (SMS 201-995) 300-500 μg/day subcutaneously for ≤9 months	No changes in ACTH or tumor size

RESULTS

Nelson syndrome

Case 1

The patient had basal ACTH level of 235.0 ± 2.2 pM and started on oct-lar (20 mg/month intramurally) while on hydrocortisone 20 mg/day and fludrocortisone 0.1 mg/day. At 18 and 21 months on oct-lar, ACTH level decreased to 116.0 ± 2.9 and 71.0 ± 4.0 pM, respectively (P = 0.0001). Pigmentation decreased, visual field remained unchanged, and there were no signs or symptoms of tumor growth. Oct-lar was discontinued to evaluate if the reduction in ACTH levels was due to the effect of radiotherapy delivered 24 months before. At 3 months of oct-lar, ACTH (266.0 ± 1.1 pM) was significantly higher than in basal conditions (P = 0.0001), proving the inhibitory effect of this drug (Fig. 1).

Cushing disease

Case 2

In this patient, basal UFC and ACTH levels were 440.0 ± 55.0 nM per day and 12.98 ± 0.9 pM, respectively. After 4 monthly injections of oct-lar, no significant differences were found either in UFC of 358.0 ± 27.0 nM per day or ACTH level of 14.5 ± 3.8 pM ($P \geq 0.090$) (Figs. 2A, B).

Case 3

In patient 3, after 4 months of oct-lar, neither UFC (649.0 ± 41.0 nM/d) nor ACTH (18.7± 3.0 pM) differed from baseline (580.0 ± 38.0 nM/d and 18.3 ± 1.8 pM, respectively) ($P \geq 0.767$) (Figs. 2A, B).

Quality of life

Table 1 displays individual data on all SF-36 domains. After 21 months on oct-lar, patient 1 achieved control threshold values in all domains. At 3 months off, the patient remained stable, although disabling symptoms related to physical function started to show off. By contrast, both patients with CD remained below the control threshold values along the trial.

DISCUSSION

To our knowledge, this is the first report on the effect of oct-lar on hormonal levels and quality of life in patients with NS and CD who failed conventional therapy.

In this study, chronic administration of oct-lar in a patient with NS showed significant reduction of

Table 3. Literature review on subcutaneous octreotide in CD.

Author	Patients, n	Medical therapy	Results
Lamberts et al[8]	3	Octreotide (SMS 201-995) 300 μg/day subcutaneously for 2 years	No changes in ACTH levels
Invitti et al[12]	3	Octreotide (SMS 201-995) 400–1200 μg/day subcutaneously for 24–49 days	ACTH/cortisol biphasic pattern (rise and return to initial values)
Ambrosi et al[13]	4	Octreotide (SMS 201-995) 100 μg subcutaneously for acute administration	No changes in ACTH levels
Stalla et al[14]	5	Octreotide (SMS 201-995) 100 μg subcutaneously for 30 and 180 minutes after cannulation of 100 μg of cubital vein CRH intravenously	No changes either on basal or CRH-stimulated ACTH and cortisol levels

CRH, corticotropin releasing hormone.

plasma ACTH levels, reaching values of <50% and 70% from baseline at 18 and 21 months, respectively, without evidence of tumor growth and side effects. Her mental and physical health improved, rendering a better quality of life that allowed her to resume her work as a teacher. When oct-lar was discontinued, ACTH levels increased significantly. Disabling physical and mental health signs became evident.

By contrast, this drug failed to control ACTH secretion in 2 patients with recurrent CD who persisted with impairment in all measures of quality of life (physical limitations, bodily pain, reduced vitality, and emotional lability).

Normal and tumoral pituitary corticotropic cells express sst_2 and sst_5; of which, sst_5 is the predominantly expressed receptor subtype. SS inhibits pituitary ACTH secretion in vitro but primarily in the absence of glucocorticoids. In pathological conditions of low endogenous cortisol level (ie, in patients with adrenal insufficiency and in patients with NS), SS and sst_2-preferring SSA (such as octreotide) are able to lower circulating ACTH.[3] In 1975, Tyrrell et al[1] demonstrated for the first time that when administered as a 1-hour infusion to 5 patients with NS, SS resulted in a sustained progressive decrease in plasma ACTH in each patient to 40%–71% of basal values with a return toward initial levels after cessation of the infusion. Thereafter, few and different results on the action of subcutaneous SSA octreotide on NS were reported (Table 2). In addition, SS and octreotide (SMS 201-995) could acutely decrease plasma ACTH levels in conditions of hypocortisolemia, such as untreated Addison disease.[20,21] However, clinical studies failed to demonstrate efficacy of octreotide in patients with CD in which circulating levels of cortisol are high. The lack of clinical efficacy of SSA octreotide in CD is likely due to the downregulation of sst_2 receptors by glucocorticoids (Table 3).

Pasireotide, a new SSA, has more affinity for sst_5 that are not downregulated by glucocorticoids and is able to reduce ACTH secretion in the presence of high concentrations of glucocorticoids.[7,22] Unfortunately, this drug is not commercially available in Argentina for clinical purposes.

The usefulness of this long-acting compound in the treatment of CD and its impact on the quality of life has not been described. In these 2 patients with persistent CD, oct-lar did not control hormonal excess, and their poor quality of life remained unchanged. As SSt_2 receptors are downrgulated by glucocorticoids, trials with oct-lar in combination with adrenostatic drugs in CD are in progress in our Unit.

We consider that oct-lar is helpful as a medical coadjuvant for primary surgical and radiotherapeutic approaches in NS contributing to control ACTH levels without side effects and helping to restore an acceptable quality of life.

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