

Our Long Term Experimentation with Slow Release Octreotide Therapy in our Acromegalic Patients and Anusual Side Effect: Hypoglycemia

Semin Melahat Fenkci

Yurdaer Sermez

Güzin Yaylalı

Pamukkale University Faculty of Medicine, Endocrinology and Metabolism, Denizli, Turkey

Octreotide is a somatostatin analog that inhibits GH and currently has been effectively used in acromegalic patients. The objective of present study was to establish the long term effects of somatostatin: the clinical response, tumor size, GH, IGF-I concentrations and side effects. We also report a severe hypoglycemic attack in an acromegalic patient whose GH levels were within the normal limits.

12 patients with acromegaly [8 females (median age 40.2±6,4 yr), 4 males (52,5±7,2 yr)] were prospectively evaluated after a mean follow –up of 24,8±17 months (6-58 months) on sandostatin –LAR.

Mean GH decreased from 18, 3±11, 1 ng/ml to 5, 8±4,3ng/ml (p<0, 001). GH reductions to less than 5.0 ng/mL were observed in 9 of the 12 patients (75%) and reductions to less than 2ng/mL were observed in 2 of them (16, 6%). Mean IGF-1 concentration was 1730 ±1301 ng/mL at the beginning of the study and decreased to 592±455,1 ng/mL . The difference was statistically significant (p<0,01). Baseline MRI showed macroadenomas in six patients. No increase in tumor size was observed in any patient. Tumor size decreased from 3320±4539 mm³ to 2581±3840 mm³ (p=0, 08). MRI showed empty sella in three patients. Clinical symptoms improved remarkably in all patients. Only one patient could not continue therapy because of severe hypoglycemic attacks after 20 months of sandostatin therapy.

Monthly injections of sandostatin LAR were effective to reduce GH and IGF-I levels in patients with active acromegaly. In the long term period this drug is well tolareted but we suggest that hypoglycemia should be kept in mind even if the GH levels are within the normal limits.

Keywords: Acromegaly,slow relasing octreotide,hypoglycemia

Introduction

Acromegaly is an insidious disease caused by unrestrained hypersecretion of GH and IGF-1 and it is associated with increased morbidity and reduced life expectancy, mostly due to cardiovascular disease (1). The excess mortality relates to the consequences of growth hormone (GH) hypersecretion rather than the tumor mass effects, and thus the crucial goal of treatment must be to

achieve biochemical control (2). Epidemiological studies have shown that the increased mortality associated with active acromegaly is reversed to normal rates in patients achieving safe GH levels regardless of the therapeutic approach used (2, 3).

Unfortunately, no single therapy is comprehensively successful in controlling the disease and its clinical presentations, and different treatment modes are associated with unique adverse effects and clinical disadvantages. (4) Adenectomy by an experienced surgeon is the treatment of choice for most patients with acromegaly, but because most tumors are macroadenomas, it is not possible to achieve complete excision and cure. Controversy persists as to the place of radiotherapy, be it conventional three field or stereotactic, but radiotherapy takes several years to be

Correspondence address:

Semin Melahat Fenkci

Pamukkale University Faculty of Medicine, Endocrinology and Metabolism, Denizli, Turkey

Tel :0532 684 30 01

Fax :0258 213 43 57

E-posta :sfenkci@yahoo.com

effective and patients will require medical therapy in the interim. Hence, even with the best surgeons, and, unfortunately, most patients are not operated on by dedicated pituitary surgeons, most patients will require medical treatment (5). Depot somatostatin analogs are able to reduce hormonal hypersecretion in most patients and normalize IGF-1 levels in many of them (6)

The aim of this study was to prospectively evaluate the effects of sandostatin –LAR on GH/IGF-1 levels and tumor size of our acromegalic patients.

Patients and Methods

12 patients with acromegaly [8 females (median age 40.2±6,4 yr), 4 males (52,5±7,2 yr)] attending to Endocrinology and metabolism department were prospectively evaluated after a mean follow –up of 24,8±17 months (6-58 months) on sandostatin –LAR. All of them had active disease according to the clinical picture, GH levels not suppressible to less than 1 µg/ liter by oral glucose load, and elevated age-matched IGF-I levels.

Sandostatin –LAR had been administered as adjuvant treatment in 8 patients; 8(66,7%), had been previously treated by neurosurgery , 3(25%) by radiotherapy, 2(16.6%) patients received both radiotherapy and neurosurgery and 3(25%) patients received gamma-knife.

Table 1. Clinical Characteristics of the patients

Patients	Age (year)	Sex F/M	Surgery	RT	Gama-knife	Duration of SS-LAR
1	50	M	-	-	-	18
2	48	M	+	-	-	32
3	63	M	-	-	-	42
4	36	F	+	+	-	16
5	46	F	+	+	+	58
6	43	F	+	-	-	14
7	43	F	+	-	+	47
8	46	F	+	-	-	8
9	48	M	-	-	-	6
10	40	F	+	-	-	25
11	28	F	+	-	+	19
12	50	F	-	-	-	12

Neurosurgery had been performed at least 2 months before the start of Sandostatin –LAR treatment, radiotherapy at least 1 yr before the start of Sandostatin- LAR treatment. In 3 patients Sandostatin –LAR had been the primary treatment. Pituitary magnetic resonance imaging (MRI) showed macroadenoma (invading the cavernous sinus) in 7 patients, microadenoma in 2 patients, and residual pituitary adenoma after neurosurgery in 5 patients, empty sella in 2 patients.

Methods

All patients were given subcutaneous octreotide at a dose of 0,1 mg three times daily for 3 weeks in order to test drug tolerance. The study was continued using octreotide LAR at 20 mg intramuscular injections 28 days apart for mean follow –up of 24,8±17 months (6-58 months). Thereafter, sandostatin –LAR schedule had been individually tailored with the aim to achieve normal age adjusted IGF-I levels and a mean GH less than 2.5 µg/ liter.

Control evaluations had been performed at 3-month intervals on an out-patient basis with a careful clinical evaluation (frequency and intensity of headache, paresthesias, perspiration, swelling, fatigue, arthralgia, snoring and side effects). Blood samples had been collected in the morning, GH concentrations and IGF-I had been assayed. GH determinations were performed by immunometric method with chemiluminiscense substrate range assay of 0.06-5 ng/ml and IGF-1 concentrations were analyzed by immunoradiometric (IRMA), range of 56-270 ng/mL.

Neuroradiological control had been performed before the start of treatment, at 6- months interval during the first year, and yearly thereafter with magnetic resonance imaging (MRI). On each scan the largest diameter of the tumor was measured on coronal (vertical diameter) and axial sections (anteroposterior and transverse), calculating the approximate volume of adenoma, after correction for magnification factor, as the volume of rotating ellipsoid with the formula (π [ventral x antero-posterior x transvers]/6.)(7). Liver ultrasound examination had been performed before the start of treatment and yearly thereafter.

Statistical analysis was performed by SPSS for Windows version 9.0 and $p < 0,05$ were considered statistically .

Results

Sandostatin –LAR was administered for 24,8±17 months (6-58 months). No patient was lost to follow-up and one patient had to give up the treatment because of severe hypoglycemia.

Clinical Signs

The clinical signs (headache, paresthesias, perspiration, swelling, fatigue, arthralgia, snoring) were improved in all patients.

GH concentration

Mean GH decreased from 18, 3±11, 1 ng/ml to 5, 8±4,3ng/ml ($p < 0, 001$). GH reduction to less than 5.0 ng/mL was observed in 9 of the 12 patients (75%) and less than 2ng/mL 2 of them (16,6%). No tachyphylaxis as observed throughout the study period.

IGF-1 concentration

Mean IGF-1 concentration was at the beginning of the study was 1730 ±1301 ng/mL and decreased to 592±455,1 ng/mL which was statistically significant ($p < 0,01$).

Effects of octreotide on tumor size

Baseline MRI showed macroadenomas in the six patients. No increase in tumor size as observed in any patient. Tumor size decreased from 3320±4539 mm³ to 2581±3840 mm³ ($p = 0, 08$). MRI showed empty cells in three patients.

Drug Tolerability

At the beginning of the subcutaneous therapy period we did not observe diarrhea, abdominal pain, steatorrhea, nausea or vomiting. Two patients reported flatulence and abdominal discomfort which is resolved after one week of subcutaneous treatment.

Cholelithiasis developed in 4 (33%) patients and two patients had been operated on. In one patient biliary sludge was discovered and it disappeared with ursodeoxycolic acid therapy after 6 months. Diabetes was discovered in two (16,6%) patients and in one patient insulin therapy was initiated after sandostatin therapy.

Only one patient could not continue therapy because of severe hypoglycemic attacks after 20 months of sandostatin therapy. He had a history of

gastric operation 10 years ago. Upper gastroendoscopic evaluation demonstrated that lower gastric sphincter was not intact. Hyperinsulinemia was not detected on biochemical analysis and computerized tomography of the upper abdomen did not show any mass lesion in the pancreas. However fasting insulin level was in the low limit of the reference levels. He was comatose on admission to the emergency department. His biochemical analysis demonstrated that the glucose level was 20 mg/dl, insulin 5,2 µIU/ml (6-27), growth hormone 1,7 ng/ml (0,05-5) cortisol 15,1 µg/dl (5-25). Long term glucose overload test were shown in the table 2. After withdrawal of the sandostatin therapy hypoglycemia did not recur.

Table 2. Insulin levels after 75gr glucose load of the patient.

Time	plasma glucose(mg/dl)	insulin (µU/l)
0	117	2,5
1	196	12,5
2	89	67,5
3	61	12,2
4	49	6,0

Discussion

The ideal therapy for acromegaly should restore GH hypersecretion to normal values, achieving normal IGF-I levels, and should enable control of tumor growth and reduction of its size, relieving tumor mass effects and sparing other pituitary hormones.

Somatostatin analogues, which have been in routine clinical use for 15 years, are the current gold standard of medical treatment. Somatostatin exists as 14 and N-terminal extended, 28-amino-acid cyclical peptides derived from a common gene located on chromosome 3q28. The gene is widely expressed throughout the brain, hypothalamus, gastrointestinal tract, and pancreas, and somatostatin acts in an endo-, auto-, and paracrine manner through five specific G-protein receptor subtypes that are ubiquitously distributed throughout the gastrointestinal and central nervous systems. The predominant endocrine effect of somatostatin is to inhibit the secretion of peptide hormones of the pituitary, pancreas, and gastrointestinal tract, such as GH, thyroid stimulating hormone, insulin, and glucagon. The influence

of somatostatin on GH secretion is principally mediated via receptor subtypes 2 and 5 (8).

Several studies have demonstrated similar efficacy of depot (long-acting release) and subcutaneous octreotide. Freda (9) recently reviewed all aspects of somatostatin analogue therapy for acromegaly; in a meta-analysis of published studies that included more than 300 patients, long-acting release octreotide suppressed GH to the target range in 56% of patients and IGF-I into the reference range in 66%. In our cases GH reduction to less than 5.0 ng/mL was observed in 9 of the 12 patients (75%) and less than 2ng/mL 2 of them(16,6%). The reduction of GH and IGF-I levels were statistically significant.

The ability of somatostatin analogues to induce tumor shrinkage is stimulating much interest. Early studies reported varying degrees of tumor shrinkage in as many as 30% of patients (10). However, more recent studies have demonstrated dramatic shrinkage in most patients, particularly in those patients treated with a somatostatin analogue as primary therapy (11,12). We demonstrated a 22.2% decrease of tumor volume in our patients. Bevan *et al.* (13), in a report of 27 patients treated with octreotide for 1 year as primary treatment, documented median tumor shrinkage in patients with microadenomas of 49% (range, 12–73) and 43% (range, 6–92) in those with macroadenomas. Amato *et al.* (14) reported 40% shrinkage in macroadenomas and 16% shrinkage in microadenomas over 12 months, but, importantly, no further reduction in tumor volume was seen during a second year of treatment.

Increased biliary tract dysfunction and gallstones have been associated with longterm therapy with octreotide LAR. This effect is largely related to suppression of cholecystokinin release and the reduced gall-bladder emptying (15) Cholelithiasis developed in 4(33%) of our patients and two had been operated on. In one patient biliary sludge was discovered and disappeared with ursodeoxycolic acid therapy and two patients were asymptomatic in the follow-up period. Lancranjan *et al* (16) reported that gallstone prevalence was only 6, 3% in their acromegalic patients after 12 months of sandostatin-LAR therapy. Flogstad *et al.* (17) reported the development of asymptomatic gallstones in only one of 14 treated patients for 18

months. Our prevalence was higher than these reports. Longer –term follow-up may be the reason. However Ayuk *et al* (18) reported that the gallstones developed in 5 of 22 patients with an average follow up of 41 months (range 12-89 months) on sandostatin-LAR therapy. We suggest that ursodeoxycolic acid may be effective for gallbladder disease but a long term controlled study is required.

Approximately 2% of patients with acromegaly treated with octreotide develop hypoglycaemia and about 15% develop hyperglycaemia. In our study one patient had severe hypoglycaemia and three patients (25%) developed diabetes after sandostatin therapy. Although we could not measure glucagon level, the inhibitory effect of sandostatin on the pancreatic glucagon secretion or secretin, gastrin and motilin which decrease intestinal motility may be the reason of the hypoglycemic attacks. Especially the GH level of the patient was within the normal limits. Octreotide, a long-acting somatostatin analogue, has been used to alleviate hypoglycaemia in patients with insulinomas. Transient worsening of fasting hypoglycaemia following octreotide has also been described (19). In the literature hypoglycemia with sandostatin was reported in two cases with mesenchymal tumor. This was the first report in acromegalic patients.

Somatostatin analogues are safe and generally well tolerated; although gastrointestinal symptoms (predominantly diarrhea and abdominal pain) are common but usually settle with long-term treatment. The incidence of gallstones is increased in acromegaly with the long term treatment periods and increases further with octreotide therapy to as high as 50%, although most patients are asymptomatic and intervention is unnecessary. Ursodeoxycolic acid may be alternative therapy for the patients with gallbladder sludge and microlithiasis. In our study we demonstrate that in the acromegalic patients with near normal GH levels on sandostatin treatment hypoglycemia may also be seen.

References

1. Wright AD, Hill DM, Lowy C, Fraser TR. Mortality in acromegaly. *Q J Med* Jan; **39**(153): 1-16, 1970.

2. Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK. Determinants of clinical outcome and survival in acromegaly. *Clin Endocrinol (Oxf)* **41**(1): 95-102, 1994.
3. Bates AS, Van't Hoff W, Jones JM, Clayton RN. An audit of outcome of treatment in acromegaly. *Q J Med* **86**(5): 293-9, 1993.
4. Melmed S, Jackson I, Kleinberg D, Klibanski A. Current treatment guidelines for acromegaly. *J Clin Endocrinol Metab* **83**(8): 2646-52, Review, 1998.
5. Gittoes NJ, Sheppard MC, Johnson AP, et al. Outcome of surgery for acromegaly the experience of a dedicated pituitary surgeon. *Q J Med* **92**: 741-745, 1999.
6. Stewart PM, Kane KF, Stewart SE, Lancranjan I, Sheppard MC. Depot long-acting somatostatin analog (Sandostatin-LAR) is an effective treatment for acromegaly. *J Clin Endocrinol Metab* **80**(11): 3267-72, 1995.
7. Di Chiro G, Nelson KB. The volume of the sella turcica. *Am J Radiol* **87**: 989-1008, 1962.
8. Rowles S, Paisley A, Trainer PJ. Somatostatin analogue versus growth hormone antagonist treatment for acromegaly: who should get what? *Curr Opin Endocrinol Diabetes* **10**: 265-271, 2003.
9. Freda PU. Somatostatin analogs in acromegaly. *J Clin Endocrinol Metab* **87**: 3013-3018, 2002.
10. Newman CB, Melmed S, Snyder PJ, Young WF, Boyajy LD, Levy R, Stewart WN, Klibanski A, Molitch ME, Gagel RF. Safety and efficacy of long-term octreotide therapy of acromegaly: results of a multicenter trial in 103 patients—a clinical research center study. *J Clin Endocrinol Metab* **1995**.
11. Lundin P, Eden EB, Karlsson FA, Burman P: Long-term octreotide therapy in growth hormone-secreting pituitary adenomas: evaluation with serial MR. *AJNR Am J Neuroradiol* **18**: 765-772, 1997.
12. Colao A, Ferone D, Marzullo P, Cappabianca P, Cirillo S, Boerlin V, Lancranjan I, Lombardi G. Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. *J Clin Endocrinol Metab* **86**: 2779-2786, 2001.
13. Bevan JS, Atkin SL, Atkinson AB, Bouloux PM, Hanna F, Harris PE, James RA, McConnell M, Roberts GA, Scanlon MF, Stewart PM, Teasdale E, Turner HE, Wass JA, Wardlaw JM. Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. *J Clin Endocrinol Metab* **87**: 4554-4563, 2002.
14. Amato G, Mazziotti G, Rotondi M, Iorio S, Doga M, Sorvillo F, Manganello G, Di Salle F, Giustina A, Carella C. Long-term effects of lanreotide SR and octreotide LAR on tumour shrinkage and GH hypersecretion in patients with previously untreated acromegaly. *Clin Endocrinol (Oxf)* **56**: 65-71, 2002.
15. Moschetta A, Stolk MFJ, Rehfeld JF, Portincasa P, Slee PH, Koppeschaar HP, Van Erpecum KJ, Vanberge-Henegouwen GP. Severe impairment of postprandial cholecystokinin release and gall-bladder emptying and high risk of gallstone formation in acromegalic patients during Sandostatin LAR. *Aliment Pharmacol Ther* **15**(2): 181-5, 2001.
16. Lancranjan I, Brew Atkinson A and Sandostatin LAR group. Results of a European multicentre study with sandostatin LAR in acromegaly patients. *Pituitary* **1**: 105-114, 1999.
17. Flogstad AK, Halse J, Bakke S, Lancranjan I, Marcbach P, Bruns CH, Jervell JAK. Sandostatin LAR in acromegaly patients: long term treatment. *J Clin Endocrinol and Metabolism* **82**: 23-28, 1997.
18. Ayuk J, Bates AS, Holden N, Clayton RN, Sheppard MC, Stewart PM. A prospective study of an initial cohort of 274 acromegalic patients drawn from a single health authority district in the United Kingdom. Proceedings of the 11th. International Congress of Endocrinology, Sidney 2000.
19. Stehouwer CD, Lems WF, Fischer HR, Hackeng WH, Naafs MA. Aggravation of hypoglycemia in insulinoma patients by the long-acting somatostatin analogue octreotide (Sandostatin). *Acta Endocrinol (Copenh)* **121**(1): 34-40, 1989.