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Journal of Diabetes, Metabolic Disorders & Control

Research Article
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Octreotide-LAR as primary therapy for acromegaly: a retrospective serial case

Abstract

Acromegaly is a chronic disease. We evaluated 10 patients with acromegaly who were given octreotide LAR as primary treatment for acromegaly. In these patients, we observed a 25% and 60% decrease in the levels of Insulin-like Growth Factor-I (IGF-I) at 6 and 12 months, respectively, and IGF-I normalization rates of 25% and 30% for the same time points, respectively. Comparing the decrease in IGF-I after the treatment was instituted, a significant reduction was found at 6 months ($p< 0.001$) and at 12 months ($p=0.048$). Response to therapy was dependent on tumor size and showed better results for microadenomas, with tumor shrinkage in 40%. The response to octreotide LAR therapy is satisfactory in patients with acromegaly, although it is still less effective than the results obtained with surgery. Nevertheless, octreotide LAR is an effective treatment option, particularly for patients who are clinically unable to undergo surgery.

Keywords: acromegaly, octreotide, somatostatin analogues, pituitary tumours, growth hormone

Volume 5 Issue 3 - 2018

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Received: March 26, 2018 | **Published:** May 31, 2018

Introduction

Acromegaly is a chronic disease with signs and symptoms resulting from the excess of circulating growth hormone (GH).[1–3] More than 95% of the cases are related to the presence of a GH-secreting adenoma. This hormone stimulates hepatic synthesis of the insulin-like growth factor type I (IGF-I), which is responsible for the GH-related somatic effects.[1,4] The incidence of acromegaly is approximately 3-4 cases per million population, while prevalence is around 60 cases per million population per year. This condition occurs with equal frequency in males and females, more commonly in the fourth and fifth decades.[5–7] Because of the insidious progression of acromegaly and failure to recognize its clinical manifestations, diagnosis is delayed in around 8 to 10 years after the onset of the disease.[4,8] Continued exposure to excess GH and IGF-I is related to high morbidity and mortality due to cardiovascular, respiratory, neoplastic and metabolic complications, in addition to severe functional impairment as a result of skeletal complications.[3,4,8,9] Recent evidence shows a mortality rate for acromegalic patients 1.7 times higher than that of the general population. The reverse proportion is true when GH levels are reduced to values below 2.5mcg/L, regardless of the therapy instituted.[10–12] The treatment of acromegaly aims to reduce symptoms, control tumor growth, inhibit GH hypersecretion and normalize IGF-I serum concentrations, thereby reducing acromegaly-related morbidity and mortality. Three treatment options are available: surgery, drug therapy and radiotherapy.[13] Transsphenoidal surgery (TSS) is the first-line treatment for acromegaly, since the complete resection of the adenoma regulates hormone levels and improves the alterations that compromise tissues and organs. The success of TSS depends on the neurosurgeon´s experience and skills, the size and extension of the tumor and preoperative GH levels. In patients with a microadenoma, normalization of IGF-I occurs after TSS in 75-95% of the cases. Normalization is less frequent with macroadenomas, and is found in approximately 50% of cases.[14–16] Medical treatment is often required, especially when no surgical cure is achieved and for patients at an advanced age and/or when severe comorbidity is present that contraindicates the surgery. Preoperative use of somatostatin analogs can be beneficial, as they promote tumor shrinkage and this facilitates surgical resection and attenuates the perioperative complications deriving from GH excess.[17] The medical treatment options currently available are somatostatin analogs (octreotide, lanreotide (LAN) and pasireotide); dopamine agonists (bromocriptine and cabergoline), and GH-receptor antagonist pegvisomant.[4]

Somatostatin analogs lead to GH suppression in most acromegalic patients, with control of hormonal levels in approximately 60% of the patients. In addition, they induce tumor shrinkage in 30-50% of the acromegalic patients with GH levels below 20mcg/L when administered as primary therapy.[8,17] Recent studies have shown tumor shrinkage of more than 20% of tumor volume in up to 100% of the patients treated with long-acting somatostatin analogs. The use of analogs was also successful in hormone regulation and volume reduction of residual tumor, with up to 80% of tumor shrinkage five years after the use of somatostatin analogs as primary treatment.[18,19] Dopamine agonists also have their role in the treatment of acromegaly. In patients who achieve no control using somatostatin analogs, dopamine agonists are of help and provide further reduction in GH, IGF-I and tumor volume.[20] Some other studies evaluated cabergoline as primary therapy; however, results were exceedingly discordant, ranging from 0% to 100% in the normalization of IGF-I. Cabergoline as a stand-alone treatment option shows only modest efficacy in acromegaly, with IGF-I decrease in around one third of the patients.[21] Pegvisomant is the most recent pharmacological option for acromegaly. This drug limits the GH-induced hepatic synthesis of IGF-I, thereby reducing IGF-I levels by approximately 95%. The effect of pegvisomant is only peripheral, with no tumor volume alteration, which restricts its utility-especially for patients with a large residual tumor or those for whom medical treatment is considered the first-line therapy.[22] Radiotherapy remains the third therapeutic option and is used less frequently. It is employed mostly for patients who obtained no disease control with surgery and medication.[14] Among the medical treatment options available for acromegaly, somatostatin analogs are the class of drugs

that promote the best results in controling the disease and achieving tumor size reduction.

Methods

Ten patients whose primary treatment for acromegaly was pharmacological were assessed with regard to gender, age group, baseline IGF-I levels at 6 and 12 months of treatment and tumor size pre-treatment and at 6 months. All the patients had their IGF-I concentrations measured at 6 months of treatment, and eight of them were measured for IGF-I at 12 months of treatment. The objective of the treatment was IGF-I reduction or normalization. Treatment failure was considered in patients who did not achieve a decrease in IGF-I levels. The data were statistically analyzed using the SOFA software version 1.1.6. Parameters such as means and percent calculations were evaluated, and the *t*-test for matched variables was used.

Results

The demographics are given in Table 1. Most patients (2/3) were female and had macroadenomas. Two peaks of incidence were noted: in the fourth and seventh decade of life (Table 1). All patients showed elevated IGF-I levels for their age and gender. At 6 months, reduction in IGF-levels occurred for 60% of the patients ($p<0.001$ vs. baseline). However, the decrease found in IGF-I concentrations at 6 months was not sustained at 12 months, when IGF-I reduction was 25% ($p<0.03$). Of the six patients whose IGF-I levels were lower at 6 months, four (66.7%) had elevated levels at 12 months. Regarding IGF-I normalization, we found 30% (3/10) of normal IGF-I levels at 6 months of treatment with LAR. At 12 months, the IGF-I normalization rate was 25% (2/8). The patients who showed normal IGF-I concentrations at 12 months had exhibited normalized levels already at 6 months (Tables 2) (Table 3). All the patients who showed normal IGF-I levels both at 6 and 12 months had microadenomas ($p<0.001$ vs. macroadenoma), were female and postmenopausal, with decreased estradiol levels.

Table 1 Demographics of the acromegalic patients of the neuroendocrinology outpatient clinic at the Hospital Santa Marcelina who received primary therapy with LAR

Demographics of the acromegalic patients	
Gender	
Female	7
Male	3
Age group	
31-40	1
41-50	3
51-60	2
61-70	1
71-80	3
Lesion size	
Macro	4
Micro	6
total	10

Table 2 Profile of the acromegalic patients showing IGF-I levels observed during treatment; variations in tumor volume are also shown

Patient	Gender	Age	Tumor size	Baseline IGF-I	IGF-I at 6 months	IGF-I at 12 months	Percentage of tumor reduction (%)
1	F	57	micro	518	278	234	-15
2	F	68	micro	439	212	179	-10
3	F	79	micro	629	321	218	-18
4	M	34	macro	718	652	559	0
5	M	43	macro	871	795	978	0
6	F	74	macro	654	458	524	10
7	F	53	micro	412	257	--	0
8	F	46	micro	382	225	189	0
9	F	71	micro	517	202	167	0
10	M	48	macro	694	612	--	0

However, if reduction/normalization of IGF-I levels are regarded as criteria of response to octreotide LAR, a marked response was noted at 6 months (90%), which was partially mantained at 12 months (50%) ($p= 0.027$). Regarding tumor volume, magnetic resonance imaging (MRI) studies performed 6 months after the treatment with octreotide LAR revealed that tumor size was unchanged in 50% of the cases; 10% showed tumor growth, and 40% had reduced tumor size. Of the four patients who achieved tumor size reduction, three had microadenomas and IGF-I normalization, while one had a macroadenoma and achieved reduced, not normal, IGF-I levels (Table 4).

Table 3 Efficacy of primary therapy based on IGF-I levels after 6 and 12 months of treatment

IGF-I	6 months	%	12 months	%
Reduction	6	60	2	25
Normalization	3	30	2	25
Failure	1	10	4	50
Total	10	100	8	100

*p<0.001 (baseline vs. 6 months)

**p= 0.048 (baseline vs. 12 months)

***p= 0.027 (6 months vs. 12 months)

Citation: Vasconcelos VC, Normando AP, Silva MCA. Octreotide-LAR as primary therapy for acromegaly: a retrospective serial case. *J Diabetes Metab Disord Control.* 2018;5(3):95–98. DOI: 10.15406/jdmdc.2018.05.00144

Table 4 Progression of sellar lesion in the patients who received primary treatment with LAR as seen on MRI of the sella turcica

Lesion size		
Unchanged	5	50%
Shrinkage	4	40%
Growth	1	10%
Total	10	100%

Discussion

Acromegaly is associated with high morbidity and mortality from cardiovascular, cerebrovascular, respiratory and neoplastic disease. This increased risk can be reduced and equal that of the general population if hormonal control is achieved.[3,9–12] Among the options for medical treatment, somatostatin analogs show the best results, which justifies the importance of evaluating the effectiveness of this drug as an alternative to surgical treatment. In the present study, female patients predominated (Table 1); this finding diverges from the literature, since most studies report an equal frequency of males and females. However, Peterson in an epidemiologic study in Germany, found predominance of females (54%) and Reid evaluating patients who underwent surgery in the 1980's and 1990's, also demonstrated greater disease prevalence in females (56%), which is consistent with our findings.[5,23] In general, diagnosis is established around the fourth or fifth decades of life, which was observed in the population evaluated in the present study (Table 1). This is of relevance, since, according to Parkinson, age has an influence on the levels of GH and IGF-I, with IGF-I levels decreasing around 37nmol/L/year.[8,24] Tumor size is a predictive factor of therapeutic success in acromegaly, which is greater for microadenomas. However, most patients present with macroadenomas, and this reduces the prospects of cure for these patients.[25–27] In our study, macroadenomas predominated as well (Table 1), which could be explained by a delayed diagnosis, a prominent occurrence in Brazil due to difficulties of access to the public health system.

Our findings showed that the effectiveness of LAR in reducing IGF-I levels is high at 6 months; however, this lowering is not always sustained at 12 months. The normalization rate of IGF-I with LAR was 30% at 6 months and maintained at 12 months, which suggests that normalization of IGF-I at 6 months is predictive of sustained response in terms of hormone control over the medium term (12 months). The normalization of IGF-I using LAR as primary therapy is more marked in patients with microadenomas. Reduction of tumor volume occurred in 40% of the patients with the use of LAR as primary therapy; all of these patients showed reduction in their IGF-I levels. In our study, treatment efficacy was more prominent in the female patients (2/3). Women exhibit some degree of resistance to GH and require higher replacement doses than men when a deficit is detected. Moreover, women have lower levels of IGF-I than those of men for similar GH concentrations regardless of disease activity or the implemented therapy-which explains the results in the present study. Although estrogen has an antagonistic action at the post-receptor level, inhibiting GH signaling and thereby decreasing hepatic IGF-I synthesis. The female patients in our study were postmenopausal, with decreased estradiol levels. Consequently, this excludes the possibility of estrogen levels having interfered with the IGF-I evaluation.

Conclusion

Octreotide LAR is effective in the treatment of acromegaly, as it shows significant results in terms of IGF-I reduction and normalization. However, the present results are still inferior to those observed with surgery; therefore, medical treatment should be indicated for patients who are not willing or able to undergo surgery or for cases in which surgery was not curative. Patients showing normalization of IGF-I at 6 months of treatment are more likely to maintain normal levels at 12 months. Tumor size influences the response to medical treatment, with microadenomas responding better both in the reduction of the IGF-I levels and in hormonal reduction. Presence of a microadenoma and normalization of IGF-I at 6 months of treatment with LAR are predictors of sustained biochemical control at 12 months of treatment. Patients who had their IGF-I levels reduced at 6 months-without normalization-are more likely to be unresponsive to medical treatment in 12 months.

Acknowledgements

None.

Conflict of interest

Author declares there is no conflict of interest.

Rerferences

1. Cook DM, Ezzat S, Katznelson L, et al. American Association of Clinical Endocrinologists Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly. Endocrine Practic. 2011;17(4):1–44.
2. Colao A, Lombardi G. Growth hormone and prolactin excess. Lancet. 1998;352(9138):1455–1461.
3. Colao A, Ferone D, Marzullo P, et al. Systemic complications of acromegaly: epidemiology, pathogenesis and management. Endocr Rev. 2004;25(1):102–152.
4. Neto LV, Abucham J, Araújo LA et al. Recomendações do Departamento de Neuroendocrinologia da Sociendade Brasileira de Endocrinologia e Metabologia para o diagnóstico e tratamento da acromegalia no Brasil. Arq Bras Endocrinol Metab. 2011;55(2):91–105.
5. Holdaway IM, Rajasoorya C. Epidemiology of acromegaly. Pituitary.1999;2(1):29–41.
6. Alexander L, Appleton D, Hall R, et al. Epidemiology os acromegalia in Newcastle region. Clin Endocrinol (Oxf). 1980;12(1):71–79.
7. Etxabe J, Gaztambide P, Latorre P, et al. Acromegaly: an epidemiological study. J Endocrinol Invest. 1993;16(3):181–187.
8. Donangelo I, Une K, Gadelha M. Diagnosis and treatment of acromegaly in Brazil. Arq Bras Endocrinol Metab. 2003;47(4):331–343.
9. Melmed S. Medical progress: acromegaly. N Engl J Med. 2006;355(24):2558–2573.
10. Dekkers OM, Biermasz NR, Pereira AM, et al. Mortality in acromegaly: a metaanalysis. J Clin Endocrinol Metab. 2008;93(1):61–67.
11. Holdaway IM, Bolland MJ, Gamble GD. A meta–analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. Eur J Endocrinol. 2008;159(2):89–95.
12. Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab. 2004;89(2):667–674.
13. Biermasz NR, Dekker FW, Pereira AM, et al. Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like

growth factor I measurements. J Clin Endocrinol Metab. 2004;89(6):2789–2796.

14. Melmed S, Colao A, Barkan M, et al. Guideline for acromegaly management: An update. J Clin Endocrinol Metab. 2009;94(5):1509–1517.
15. Nachtigall L, Delgado A, Swearingen B. Extensive Clinical Experience: Changing patterns in diagnosis and therapy of acromegaly over two decades. J Clin Endocrinol Metab. 2008;93(6):2035–2041.
16. Sheaves R, Jenkins P, Blackburn P, et al. Outcome of trans-sphenoidal surgery for acromegaly using strict criteria for surgical cure. Clin Endocrinol (Oxf). 1996;45(4):407–413.
17. Colao A, Ferona D, Cappabianca P, et al. Effect of octreotide pretreatment on surgical outcome in acromegaly. J Clin Endocrinol Metab. 1997;82(10):3310–3314.
18. Colao A, Auriemma RS, Galdieiro M, et al. Effects of initial therapy for five years with somatostatin analogs for acromegaly on growth hormone and insulin-like growth factor-I levels, a prospective study. J Clin Endocrinol Metab. 2009;94(10):3746–3756.
19. Baldelli R, Colao A, Razzore P, et al. Two-year follow-up of acromegalic patients treated with slow release lanreotide (30 mg). J Clin Endocrinol Metab. 2000;85(11):4099–4103.
20. Roger ABS, Verhelst J, Maiter D, et al. Cabergoline in the treatment of acromegay: a study in 64 patients. J Clin Endocrinol Metab. 1998;83(2):374–378.
21. Sandret L, Maison P, Chanson P. Place of Cabergoline in Acromegaly: A Meta-Analysis. J Clin Endocrinol Metab. 2011;96(5):1327–1335.
22. Sherlock M, Woods C, Sheppard MC. Medical therapy in acromegaly. Nat Rev endocrinol. 2011;7(5):291–300.
23. Nabarro JD. Acromegaly. Clin Endocrinol (Oxf.). 1987;26(4):481–512.
24. Parkinson C, Renehan AG, Ryder WD. Gender and age influence the relationship between serum GH and IGF-I in patients with acromegaly. Clin Endocrinol (Oxf). 2002;57(1):59–64.
25. Giustina A, Chanson P, Bronstein MD, et al. A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab. 2010;95(7):3141–3148.
26. Feelders RA, Hofland LJ, van Aken MO, et al. Medical therapy of acromegaly: efficacy and safety of somatostatin analogues. Drugs. 2009;69(16):2207–2226.
27. Colao A, Cappabianca P, Caron P, et al. Octreotide LAR vs. surgery in newly diagnosed patients with acromegaly: a randomized, open-label, multicentre study. Clin Endocrinol (Oxf). 2009;70(5):757–768.

Citation: Vasconcelos VC, Normando AP, Silva MCA. Octreotide-LAR as primary therapy for acromegaly: a retrospective serial case. *J Diabetes Metab Disord Control.* 2018;5(3):95–98. DOI: 10.15406/jdmdc.2018.05.00144