



Curative Result with Primary Medical Therapy in an Elderly Acromegaly Patient

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Abstract

In acromegaly, transsphenoidal hypophysectomy is the primary treatment of choice. Medical treatment is performed on patients uncontrollable with surgery. Indications for primary medical treatment or medical treatment prior to surgery are limited to patients with macroadenoma with high risk for surgery due to cardiac and respiratory problems. Medical treatment is not applied on patients with microadenoma due to the high chance of cure with surgical option. Seventy-five years-old female patient was admitted in our clinic with complaints of drowsiness, fatigue and growth in hands and feet. Patient's IGF1 level was measured 516 ng/ml (64-188 ng/ml normal range for age and gender) and in the magnetic resonance imaging of the pituitary; an adenoma, 2x2 mm in size, was detected. Octreotide LAR therapy was begun 10 mg per month considering the age of the patient. IGF1 level was measured as 129ng/ml and growth hormone (GH) as 0.65ng/ml (0.06-5 ng/ml normal range) at the end of the third month of treatment. On the MRI carried out in the 9th month of treatment, it was observed that the pituitary was compatible with partial empty sella and no adenoma was determined. In our case of acromegaly with microadenoma, taking into account the age and medical condition of the patient, primary medical therapy was required. Although a low dose of octreotide LAR was implemented, primary medical therapy has been effective in controlling biochemical parameters. Moreover, it was observed that the tumor completely disappeared and is considered a curative result. Therefore, primary medical treatment of acromegaly should be among the options in selected patients with microadenomas.

Key words: Acromegaly, primary medical treatment, octreotide, elderly patient

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Introduction

Growth hormone-secreting pituitary tumors are almost always of benign nature and although an aggressive growth pattern is seen in some of these tumors, they often do not develop into true malignant tumors that cause metastasis. However, acromegaly is associated with the risk of serious morbidity and mortality due to the cardiovascular, respiratory, endocrine pathologies induced by increasing growth hormone (GH) and insulin-like growth factor 1 (IGF1) levels [1]. Treatment goals of acromegaly can be listed as normalization of GH and IGF1 levels, complete removal of tumor, a significant reduction in tumor size or prevention of tumor growth, ensuring normal pituitary functions, reduction of co-morbidities, improved quality of life and reduce the risk of mortality [2-3]. Three approaches in treatment are surgery, medical treatment and radiotherapy. Each of these approaches has their own pros and cons, however; the appropriate application of these treatments reduces the mortality risk of the patient population [3]. Transsphenoidal surgery (TSC) approach is the primary treatment of choice in acromegaly. Patients that transphedonial surgery is appropriate for can be summarized as acromegaly patients with intrasellar microadenomas and patients with noninvasive macroadenomas or macroadenomas with compression and no co-morbidities [1]. In patients with microadenomas, surgery has a high chance of success for complete tumor removal and provides with normalization of IGF-I and GH levels in 75–95% of patients. However, in macroadenomas, during biochemical controls, the normalization of IGF-1 is indicated to be about 30% and this situation constitutes a need for medical adjuvant treatment [4]. Medical treatments prior to surgery or primary indications are limited to patients with risk for surgery due to cardiac and respiratory problems in patients with macroadenoma. Medical treatment is not preferred because patients with microadenoma have a high chance of cure with surgery and it is controversial before surgery to positive contribution to the course of disease in macroadenomas. Although often needed in medical treatment as adjuvant, conventional fractionated radiotherapy, stereotactic radio-surgery (Gamma Knife surgery included), Cyber Knife treatment or radiotherapy in the form of proton-beam is less needed in patients with acromegaly [5].

Options that medical treatment is appropriate can be listed as follows: [1];

- First-line treatment; in cases where surgery has a low chance of cure (i.e. extrasellar large tumors without signs of compression) to ensure that the tumor shrinks before surgery [6-8],
- After surgery; in cases of biochemical control cannot be achieved [9],
- Before surgery; to reduce the complications of operation by ensuring the healing of serious co morbid conditions (not proven) [10],
- In patients who underwent radiotherapy; to ensure that the disease is under control until the time that the effect of radiotherapy can be seen [11].

Somatostatin analogues are the first of choice of medicine in medical treatment [4]. Two somatostatin analogues that are currently in use, octreotide and lanreotide are the main agents for the treatment of acromegaly. Both of the long-acting somatostatin analogues (SA) appear to have similar effects for symptom control and normalization of GH or IGF1 levels in well-designed studies [9]. Somatostatin analogs effectively reduce the high GH and IGF1 levels in acromegaly, however; information about ensuring significant reduction in tumor size is limited. While a clinically evident tumor shrinkage is observed with patients on octreotide, it is stated that tumor shrinkage is observed in 37% of patients on lanreotide. [12-13].

With the presented facts in this report; the curative result on an elderly patient, who was started primary medical treatment, was aimed to be evaluated from a primary medical treatment perspective in light of literature review.

Case

Seventy-five years old female patient was admitted to our clinic with complaints of sleepiness, fatigue, growth in hands and feet. The patient, who has 10 years of hypertension and 3 years of diabetes history, was treated with oral agents. In the systematic examination, an increase in the interdental spaces, slight prognathism, and findings of bilaterally degenerative arthritis of the knees with slightly more pronounced arch were present. Apart from this, patient was diagnosed with Alzheimer's disease by the department of neurology and medical

treatment has been in practice. Hyperglycemia and hyperlipidemia were present in patient's first examinations (Table 1). Acromegaly was presumed due to the clinical findings and hormone tests were performed. IGF1 and GH levels were measured 516 ng/ml (64-188 ng/ml normal range for age and gender) and 2.5 ng/ml (0.06-5 ng/ml normal range) and oral glucose tolerance test was performed for GH suppression. It was observed that GH levels were not suppressed with nadir GH level as 2.1 ng/ml (Figure 1). Magnetic resonance imaging (MRI) of the pituitary revealed an intrasellar adenoma, 2x2 mm in size. In the thyroid ultrasound, there were some iso-echoic nodules, the largest one being 15 mm in diameter (fine needle aspiration biopsy has not been performed because age of patients and lack of malignant properties with ultrasound); fecal occult blood test was negative, abdominal and thoracic imaging studies were negative for malignancy. Surgery was not performed taking into consideration the age and poor cooperation of the patient due to Alzheimer's disease and octreotide LAR therapy was begun to the patient with a dose of 10 mg intramuscularly once a month. IGF 1 level was found 129 ng/ml and growth hormone was found 0.65 ng/ml at the end of the third month of treatment (Figure 2). On the MRI carried out in the 9th month of treatment, it was observed that the pituitary was compatible with partial empty sella and no adenoma was determined (Figure 3). IGF1 levels have stayed within the range 90-120 ng/ml for two years with medical therapy (Figure 2). Patient was considered to be cured and treatment was discontinued after two years and IGF1 levels have stayed within the range 90-120 ng/ml for six months after discontinuation of therapy.

Table 1. The patient's laboratory values before and after treatment.

Date	0	6 th month
Glucose (mg/dl)	189	118
ALT (U/l)	18	22
Creatinin (mg/dl)	0.9	0.8
Chol (mg/dl)	270	255
LDL (mg/dl)	198	169
HDL (mg/dl)	45	46
Trig (mg/dl)	135	200
HbA1c %	6.7	6.1
Hb (g/dl)	13.4	12.8
MCV(fL)	97	88
ESR (mm/hour)	34	26
TSH (mU/ml)	1.483	1.020
FSH (mU/ml)	52.3	36.2
Prolactin (ng/ml)	11.2	8.7
GH (ng/ml)	2.5	0.6
IGF1 (ng/ml)	516	129
Femur T score	-1.8	-1.7
L1-4 T score	-3.0	-2.7

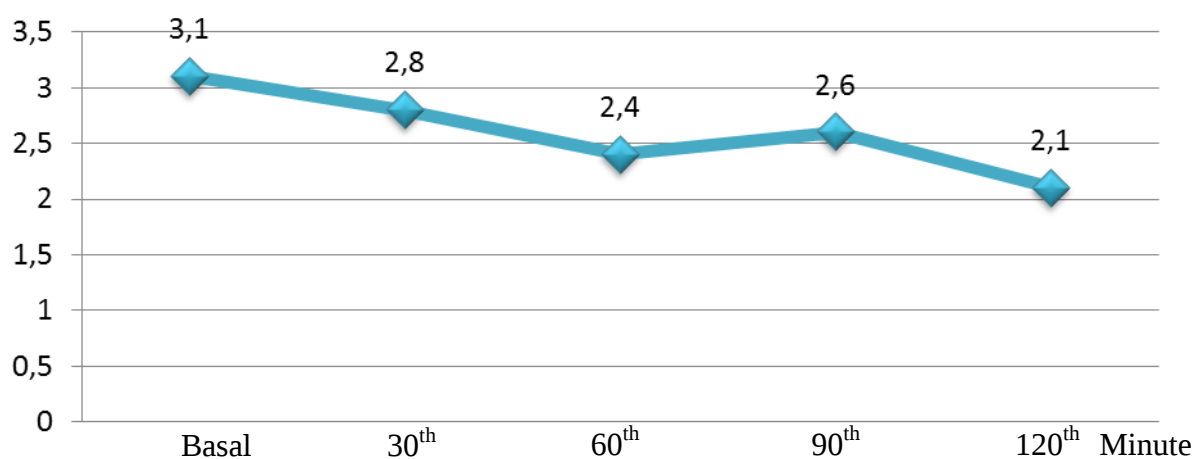


Figure 1. Patients suppression of GH with the oral glucose tolerance test results (0-120th min). Gh values are ng/ml.

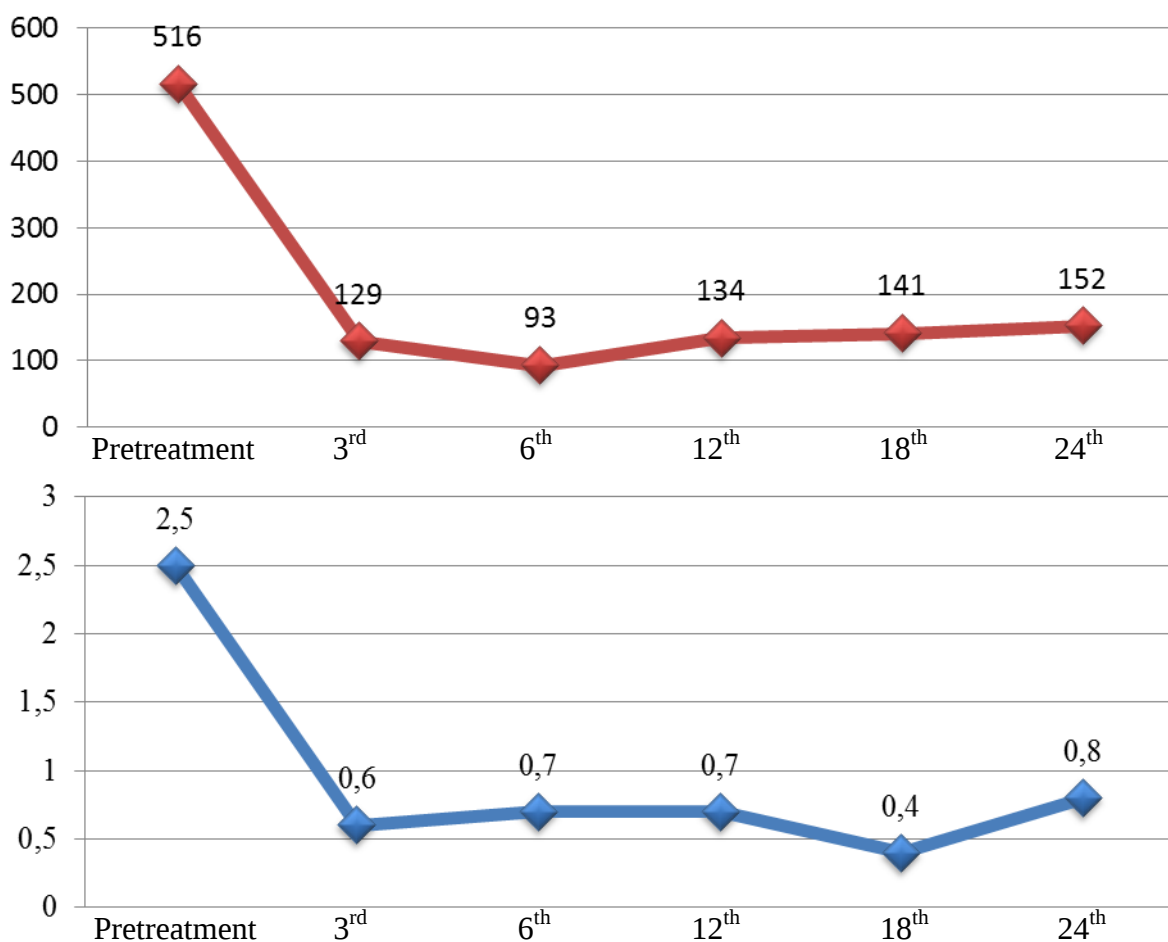


Figure 2. IGF1 (ng/ml) and GH (ng/ml) values in the follow up of the patient (0-3-6-12-18 and 24th months).

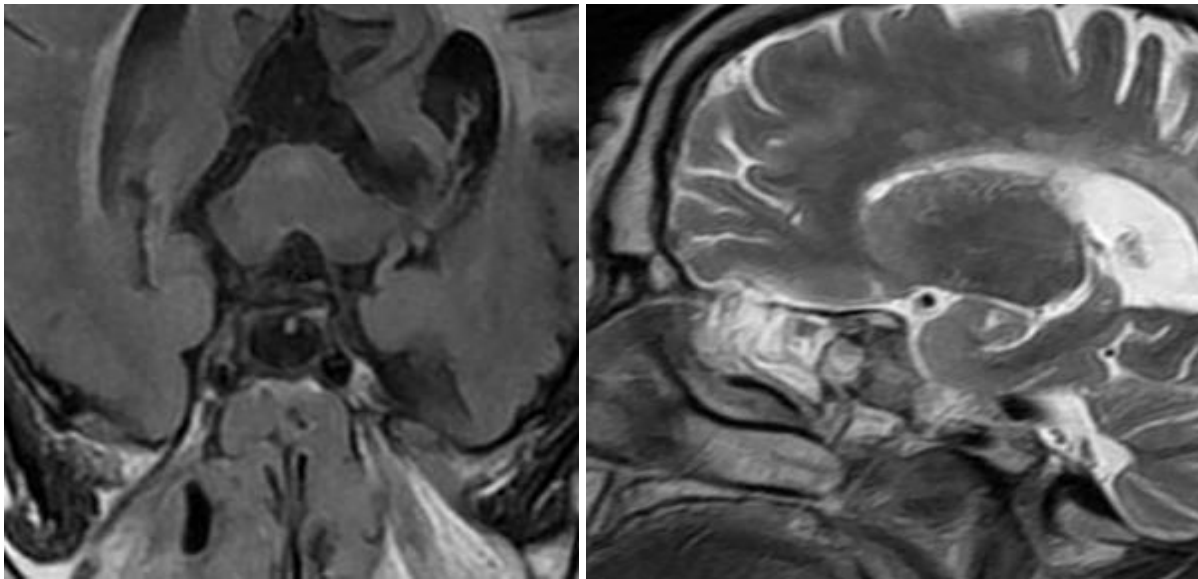


Figure 3. MRI images of patient in the 9th month of treatment. The pituitary was compatible with partial empty sella and no adenoma was determined.

Discussion

In terms of biochemical control and tumor shrinkage, SA therapy has been reported with success rates of 50-75% among patients in the studies evaluating pre-surgical medical treatment results [7-8,14-18].

Cozzi et al reported that the normalization of GH and IGF1 has been achieved in 68% and 70% of patients and 82.1% of the patients showed tumor shrinkage with an average of 62.1% by SA therapy. In this study with a 48-month follow-up period on average, 3 of 64 patients had complete resolution of the tumor and the cavernous sinus invasion was resolved in another three patients with SA therapy [7]. In the study of Coloa et al with 99 patients and with a 12-month duration, GH and IGF1 control were achieved in 57.6% and 45.5% of the patients respectively, in 78.8% of patients showed varying degrees of tumor shrinkage and the decrease in IGF1 levels has been reported as the best indicator for tumor shrinkage [8]. In another study of Maize et al, results of primary medical therapy in 36 patients over a duration of 8 years on average with acromegaly have been published and more than 20% tumor shrinkage has been reported in 72% of the patients [18].

Similar results were obtained in other studies, however; patients mentioned in the studies mostly consist of ones with invasive or macroadenomas. There is no study for patients with microadenomas. In Maize's study, 8 of 36 patients were reported to have microadenomas. According to the article, it was seen that two patients had tumor shrinkage more than 20% in size and two had less than 20%. There were no data for the other four patients [18]. In Coloa's study, 13 of 99 patients were reported to have microadenomas. Reduction in tumor size was reported to be 30.4% in patients with microadenomas and 28.3% in patients with macroadenomas in this study and tumor size reduction has been reported to be non-associated with tumor size [8]. On the other hand, in the Bevan et al study, tumor shrinkage was reported to be higher in patients with microadenomas than those with macroadenomas [19]. However; in general, the most influential determinant of tumor shrinkage has been reported as the decrease in IGF1 levels. In our patient, a 75% reduction in IGF1 levels was achieved at the end of the third month of the treatment and, GH and IGF1 normalization was observed in the early period. Significant tumor shrinkage (>75%) was reported in 4 of the 27 (14.8%) patients receiving octreotide and lanreotide in the study of Carlsen et al and the positive impact of early responses on treatment outcomes have been noted [17].

There are also some randomized prospective studies to compare the results of surgical and medical treatment in the literature. In one of them, Caloa et al compared 104 patients with acromegaly due to macroadenomas in terms of medical and surgical treatment. In the 48-month follow-up period, tumor shrinkage was found in 73% of patients receiving medical therapy and in 95% of surgically treated patients. Overall treatment success in both groups was found to be 28% and 39% respectively [20]. In the study reported from Turkey by Karaca et al with a total of 22 acromegaly patients with macroadenomas, it was found that biochemical control rate at the end of 12 months was 27% in the medical treatment group and 64% in the surgical group. Tumor shrinkage has been reported as 31% in medical therapy and 79% in surgical therapy [21]. Studies comparing surgical and medical treatment in the acromegaly patients with microadenomas are not available in the literature yet, to our knowledge. However, success rates with surgical treatment are reported as over 80% [4]. The effect of medical treatment before surgery in the microadenomas to the outcome of surgical treatment was examined by Carlsen et al. and in this study with 10 patients, one of the five patients receiving medical therapy before microadenomas and three of the five patients who underwent direct surgical treatment were reported to be cured [10]. Therefore, surgical

treatment option in patients with microadenomas is limited to the data from studies examining the results of surgical treatment there are no comparable results with medical and surgical treatment in microadenomas. In our case, medical treatment was begun although the patient has microadenoma considering the risk of surgery due to advanced age of the patient. Curative results both biochemically and in terms of tumor size were observed. The pre-treatment tumor size detected is 2x2 mm in our case and can be stated as an early diagnose of acromegaly according to the clinical findings. The findings about tumor size, age at diagnosis, gender are contradictory as factors affecting the results of treatment. However, in our case with a small tumor size and early diagnosis based on clinical findings, it can be claimed that a higher chance of cure with medical therapy can be stated in such cases. However; there are no data to support our opinion in the literature. More of these patients will increase the likelihood of early diagnosis by increasing the awareness of acromegaly among physicians. In theory, in patients with microadenomas under five mm in size, comparable results of primary medical therapy with surgery should be considered as a subject to be explored judging by the curative result obtained in our case.

References

1. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Laws E, Schlechte J, Vance ML, Ho K, Giustina A; Acromegaly Consensus Group. Guidelines for acromegaly management: an update. *J Clin Endocrinol Metab.* 2009;94(5):1509-17.
2. Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP. Mortality in acromegaly: a metaanalysis. *J Clin Endocrinol Metab.* 2008;93(1):61-7.
3. Kauppinen-Mäkelin R, Sane T, Reunanen A, Välimäki MJ, Niskanen L, Markkanen H, Löyttyniemi E, Ebeling T, Jaatinen P, Laine H, Nuutila P, Salmela P, Salmi J, Stenman UH, Viikari J, Voutilainen E. A nationwide survey of mortality in acromegaly. *J Clin Endocrinol Metab.* 2005;90(7):4081-6.
4. Schöfl C, Franz H, Grussendorf M, Honegger J, Jaursch-Hancke C, Mayr B, Schopohl J; participants of the German Acromegaly Register. Long-term outcome in patients with acromegaly: analysis of 1344 patients from the German Acromegaly Register. *Eur J Endocrinol.* 2012;168(1):39-47.
5. Andersen M. Management of endocrine disease: GH excess: diagnosis and medical therapy. *Eur J Endocrinol.* 2013;170(1):R31-41.
6. Melmed S, Sternberg R, Cook D, Klibanski A, Chanson P, Bonert V, Vance ML, Rhew D, Kleinberg D, Barkan A. A critical analysis of pituitary tumor shrinkage

during primary medical therapy in acromegaly. *J Clin Endocrinol Metab.* 2005;90(7):4405-10.

7. Cozzi R, Montini M, Attanasio R, Albizzi M, Lasio G, Lodrini S, Doneda P, Cortesi L, Pagani G. Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. *J Clin Endocrinol Metab.* 2006;91(4):1397-403.
8. Colao A, Pivonello R, Auriemma RS, Briganti F, Galdiero M, Tortora F, Caranci F, Cirillo S, Lombardi G. Predictors of tumor shrinkage after primary therapy with somatostatin analogs in acromegaly: a prospective study in 99 patients. *J Clin Endocrinol Metab.* 2006;91(6):2112-8.
9. Murray RD, Melmed S. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. *J Clin Endocrinol Metab.* 2008;93(8):2957-68.
10. Carlsen SM, Lund-Johansen M, Schreiner T, Aanderud S, Johannesen O, Svartberg J, Cooper JG, Hald JK, Fougner SL, Bollerslev J; Preoperative Octreotide Treatment of Acromegaly study group. Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. *J Clin Endocrinol Metab.* 2008;93(8):2984-90.
11. Bex M, Abs R, T'Sjoen G, Mockel J, Velkeniers B, Muermans K, Maiter D. AcroBel--the Belgian registry on acromegaly: a survey of the 'real-life' outcome in 418 acromegalic subjects. *Eur J Endocrinol.* 2007;157(4):399-409.
12. Giustina A, Mazziotti G, Torri V, Spinello M, Floriani I, Melmed S. Meta-analysis on the effects of octreotide on tumor mass in acromegaly. *PLoS One.* 2012;7(5):e36411.
13. Mazziotti G, Giustina A. Effects of lanreotide SR and Autogel on tumor mass in patients with acromegaly: a systematic review. *Pituitary.* 2010;13(1):60-7.
14. Auriemma RS, Pivonello R, Galdiero M, De Martino MC, De Leo M, Vitale G, Lombardi G, Colao A. Octreotide-LAR vs lanreotide-SR as first-line therapy for acromegaly: a retrospective, comparative, head-to-head study. *J Endocrinol Invest.* 2008;31(11):956-65.
15. Colao A, Auriemma RS, Galdiero M, Lombardi G, Pivonello R. Effects of initial therapy for five years with somatostatin analogs for acromegaly on growth hormone and insulin-like growth factor-I levels, tumor shrinkage, and cardiovascular disease: a prospective study. *J Clin Endocrinol Metab.* 2009;94(10):3746-56.
16. Carlsen SM, Svartberg J, Schreiner T, Aanderud S, Johannesen O, Skeie S, Lund-Johansen M, Fougner SL, Bollerslev J; POTA study group. Six-month preoperative octreotide treatment in unselected, de novo patients with acromegaly: effect on biochemistry, tumour volume, and postoperative cure. *Clin Endocrinol (Oxf).* 2011;74(6):736-43.
17. Li ZQ, Quan Z, Tian HL, Cheng M. Preoperative lanreotide treatment improves outcome in patients with acromegaly resulting from invasive pituitary macroadenoma. *J Int Med Res.* 2012;40(2):517-24.
18. Maiza JC, Vezzosi D, Matta M, Donadille F, Loubes-Lacroix F, Cournot M, Bennet A, Caron P. Long-term (up to 18 years) effects on GH/IGF-1 hypersecretion and

tumour size of primary somatostatin analogue (SSTa) therapy in patients with GH-secreting pituitary adenoma responsive to SSTa. Clin Endocrinol (Oxf). 2007;67(2):282-9.

19. Bevan JS1, 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. 2002;87(10):4554-63.
20. Colao A, Cappabianca P, Caron P, De Menis E, Farrall AJ, Gadelha MR, Hmissi A, Rees A, Reincke M, Safari M, T'Sjoen G, Bouterfa H, Cuneo RC. Octreotide LAR vs. surgery in newly diagnosed patients with acromegaly: a randomized, open-label, multicentre study. Clin Endocrinol (Oxf). 2009;70(5):757-68.
21. Karaca Z, Tanriverdi F, Elbuken G, Cakir I, Donmez H, Selcuklu A, Durak AC, Dokmetas HS, Colak R, Unluhizarci K, Kelestimur F. Comparison of primary octreotide-lar and surgical treatment in newly diagnosed patients with acromegaly. Clin Endocrinol (Oxf). 2011;75(5):678-84.