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# Pegvisomant therapy in acromegalic patient resistant to other treatment: case report

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## Abstract

**Introduction:** Acromegaly is a chronic, rare disorder resulting from growth hormone (GH) hypersecretion, usually caused by a pituitary adenoma. GH stimulates synthesis of insulin-like growth factor 1 (IGF-1), whom assay should be used as a screening test whenever acromegaly is suspected. Patients with acromegaly normally take from 5 to 10 years to receive a correct diagnosis, leading to complications such as cardiovascular, respiratory, and endocrine problems that are

responsible for an increase mortality. Late diagnosis of the disease also impact the effectiveness of surgical, pharmacological and radiotherapy treatment.

**Case report:** A 33-year-old acromegalic man with pituitary macroadenoma resistant to therapy of somastatin analogue (octreotide, lanreotide) and dopamine agonist (cabergoline). The patient underwent transsphenoidal adenomectomy, after wich high level of GH and IGF-1 were still measured. Due to the lack of the effect of the current treatment, the patient was qualified for pegvisomant therapy, as a result of which biochemical control was achieved without adverse events and with a good compliance of treatment.

**Conclusions:** Treatment with pegvisomant is now an important therapeutic strategy to achieve full disease control in acromegalic patients resistant or poorly responders to first generation somatostatin receptor ligands and in patients who do not respond adequately to selective excision of pituitary adenoma and /or for whom surgery is not possible.

**Key words:** acromegaly; treatment; pegvisomant; pituitary macroadenoma;

**Introduction:** Acromegaly is a rare, chronic disease characterized by excess levels of circulating growth hormone (GH), usually caused by a pituitary adenoma. Excessive secretion of GH leads to excessive production of insulin-like growth factor 1 (IGF-1) from the liver and systemic tissues[1]. Increased IGF-1 activity leads to changes in the patient's appearance - enlargement of the acral part (hands, feet, face), hypertrophy of soft tissues and organs internal and a number of systemic complications that reduce the quality of life and survival of the patient[2].

The prevalence of acromegaly is estimated at approximately 3-14 cases per 100,000 inhabitants and the annual incidence rates range between 0,2-1,1 cases per 100,000 people per year across the world. In both males and females acromegaly is diagnosed in their 40s–50s. The disease is usually diagnosed only 5–10 years (later in males) after the onset of first signs and symptoms, leading to the appearance of complications such as cardiovascular, respiratory, and neoplasia problems that are responsible for an increase of mortality[3,4].

In order to assess disease control, blood levels of GH and IGF-1 are measured[1]. The tools to control the disease are surgical treatment, pharmacotherapy, or less frequently radiotherapy[5].

Trans-sphenoidal surgery is the first-line procedure for the treatment of acromegaly. The effectiveness and success of surgical treatment of somatotrophic pituitary tumours depend on tumor size. Surgical success is achieved in patients with microadenomas (GH < 1.0 µg/L) approximately in 70–90% of patients, while in the case of macroadenomas – only in about 30–50%[6]. Since most tumors at diagnosis of acromegaly are macroadenomas, pharmacological treatments are needed. Medical therapy is routine used preoperative, but also used when surgery is not recommended or when the patient refuses to undergo surgical procedures. The drug options for controlling GH and/or IGF-1 levels are long-acting somatostatin receptor ligands (SRLs), dopamine agonists (usually cabergoline) and the GH receptor antagonist [pegvisomant (PEG)][7]. The treatment of choice in acromegaly is SRLs to which we include: Lanreotide Autogel and Octreotide LAR[5]. The effectiveness of first-generation somatostatin analogues is influenced by many components, among others sex (better response in females), age at diagnosis (younger individuals tend to have more aggressive tumours), disease duration, adenoma size and GH secretion[8]. If the effectiveness of the somatostatin analog is insufficient, it should be included dopamine agonists or GH receptor antagonist (pegvisomant)[9]. Dopamine agonists are less effective in treating acromegaly (cabergoline normalises IGF-1 concentration in about 35% of patients), than PEG (which has been shown to control acromegaly in 60–90% of patients across several clinical trials)[2,6]. Pegvisomant, normalises IGF-1 levels, by blocking GH activity in target tissues, thus reducing systemic complications and clinical symptoms. Although PEG improves the quality of patients' life and corrects metabolic disorders, it does not affect the size of the pituitary tumor, so its volume must be controlled during treatment[10]. Therapeutic strategy to achieve full disease control in acromegalic patients resistant or poorly responders to SRLs, nowadays is represent by PEG as monotherapy or in association with SRLs[1].

**Case report:** A 33-year-old man with clinically evident acromegaly was referred to the Department of Endocrinology and was admitted for the hormonal evaluation of the hypothalamic-pituitary system 3 years ago. The typical symptoms of acromegaly, including increased sweating, headaches, enlargement of the hands and feet, and thickening of facial features, have been observed by the patient for about 5-6 years. The patient was diagnosed with arterial hypertension and denied other symptoms, such as galactorrhea, signs and symptoms of diabetes mellitus. In a clinical trial, the patient showed a pronounced acromegalic phenotype with protruding eyebrows, nasal enlargement, thickening of the lips, macro-linguistic prognathism, acral enlargement, obesity (BMI: 29,9) and persistent high blood pressure resistant to the treatment.

Initial testing revealed IGF-1 >1600.0 ng/l (normal:114,0 - 247,0), basal-GH 171.400 ng/ml (normal:0,030 - 2,470) without inhibition in OGTT, prolactin 13.6 ng/ml (normal:2,10 - 17,70),

total testosterone 90.39 ng/dl (normal: 165,0 - 753,0), parathyroid hormone 23.0 pg/ml (normal:18,4 - 80,1), normal gonadotropins, adrenal and thyroid function. In the performed OGTT test - normoglycemia, but with coexisting insulin resistance (HOMA-IR = 5.22). An increase in total cholesterol (197 mg/dl N:115 - 190), triglycerides (250 mg/dl N:< 150) and a decrease in HDL fraction (38.00 mg/dl N: > 40,00) indicate atherogenic dyslipidemia. Magnetic resonance imaging (MRI) revealed a well-demarcated, slightly asymmetrical (with a predominantly right side) pathological mass measuring 25x20x24mm (apxcccxlr), which presses and lifts the optic chiasm upwards and lies in the immediate vicinity of the left cavernous sinus - the features of infiltration cannot be ruled out. In addition, the lesion penetrates into the sphenoid sinus. Taking into account the diagnosis of acromegaly, the first-line therapy was started in the form of a long-acting somatostatin analogue (octreotide) at an initial dose of 20 mg/month.

After 2 months of treatment, the remarkably elevated GH (121.000 ng/ml) and IGF-1 (>1600.0 ng/ml) values were still maintained, despite the resolution of nagging headaches and the reduction of soft tissue swelling. The correct function of the thyrotropic and adrenocorticotrophic axes as well as the correct concentration of prolactin was confirmed. The persistence of the insufficiency of the gonadotropic axis is noteworthy. At the time of hospitalization, a double episode of asymptomatic sinus bradycardia (HR: 40/min) was noted. ECHO of the heart showed second degree mitral valve regurgitation and left ventricular enlargement. ECG examination without significant changes. Treatment was modified by replacing octreotide LAR with Lanreotide Autogel 120 mg / 28 days.

Within 5 months of treatment with Lanreotide Autogel therapy, laboratory tests showed better but without normalization of GH levels (initially 171, now 87.57 ng/dl), IGF-1 (initially> 1600 ng/ml, 1155 ng/ml in the control) and total testosterone slightly increased (116.65 ng/dl). Persistent arterial hypertension was observed and the antihypertensive treatment was intensified. There was also hyperbilirubinemia (total bilirubin: 2.00 mg/dl N:0,30 - 1,20), most likely caused by the use of a somatostatin analogue. Taking into account the entire clinical picture, in particular the lack of alignment of laboratory parameters and the lack of improvement in well-being, it was decided to shorten the time of pharmacological preparation for surgery. A dopamine agonist - cabergoline 0.5 mg twice a week was added to pharmacotherapy.

The patient was persuaded to undergo transsphenoidal adenomectomy, without complications, in June 2020. Histologically, the tumor was classified as sparselygranulated type. Immunohistochemistry: GH (+), PRL (-), ACTH (-), TSH (-), FSH (-), LH (-), alpha subunit (-). One month after the procedure the early random-GH was 5.340 ng/ml and the evaluation after 4 months confirmed persistent disease. The test results were as follows: IGF- 875.0 ng/ml, random-

GH 5.180 ng/ml, nadir-GH 4.900 ng/ml. Additionally, laboratory tests showed the normal function of the other pituitary axes, including the gonadotropic axis and lipid profile back in the norm (total cholesterol- 135 mg/dl, HDL- 41 mg/dl, triglycerides- 67 mg/dl). MRI did not reveal any focal changes. The disease was not fully controlled, despite the reported by the patient reduction of swelling within the fingers, weight loss (BMI: 26,9), reduced sweating and headaches. The patient returned to the therapy with a long-acting somatostatin analogue (lanreotide 120mg /28 days).

In February 2021 small, decrease in hormonal levels was obtained, but without reaching the target, as follows: IGF-1- 661.0 ng/ml, basal-GH- 4.630 ng/ml. MRI showed an area of 10x3 mm in the coronal plane images, without any features of contrast enhancement after intravenous administration of a paramagnet. Due to the lack of clinical improvement in the treatment used so far and persistently elevated bilirubin values (total bilirubin:1.50 mg/dl), the patient was qualified to the drug program with pegvisomant.

In March 2021, the patient started PEG therapy with an initial daily dose of 10 mg, increased to 15 mg/day due to increased IGF-1 levels. IGF-1 levels were monitored during PEG therapy in the following months and were as follows: April- 289.0 ng/ml, May- 281.0 ng/ml, June- 282.0 ng/ml, July- 332.0 ng/ml, August- 210.0 ng/ml, September- 172.0 ng/ml, December- 218.0 ng/ml. The bilirubin level has been normalized (total bilirubin: 0,8 mg/dl). Other biochemical parameters remain unchanged. A control MRI was performed, which showed that the area described in the previous examination, in the anterior pituitary gland on the central side and on the left side, had decreased- the current size was about 8.5x2.5 mm- most likely the fluid area (postoperative changes). The body mass has been reduced to 85kg (BMI: 26,2). Blood pressure before PEG treatment was: 148/94 mmHg, during treatment it decreased: 125/78 mmHg. The patient's compliance was satisfactory throughout the whole period of treatment and no side effects were reported. During PEG treatment, the patient reports general well-being, infrequent headaches, no hyperhidrosis, normal hand mobility, no swelling. Biochemical and clinical control of the disease was achieved with PEG therapy. To date, the patient is continuing the treatment.

**Discussion:** Patients with acromegaly normally take from 8 to 10 years to receive a correct diagnosis, typically earlier in females[2]. The diagnosis of active acromegaly is based on the presence of signs and symptoms (acral enlargement, hypertrophy of the soft tissues, bones, and internal organs, glucose intolerance, reduced libido, headache and many others) and increased secretion of both IGF-1 and GH. Patients with signs suggestive of acromegaly should undergo a screening IGF-1 assay. If the levels are above the upper limit of normal (for age and sex), GH suppression in oral glucose tolerance test (OGTT) after administration of 75 g of glucose is

recommended. Active acromegaly is diagnosed when the IGF-1 level is increased and GH secretion in OGTT is not suppressed below 1.0 µg/L. A random GH level below 1.0 µg/L rules out active acromegaly. Following biochemical diagnosis, contrast enhanced magnetic resonance imaging (MRI) of the sellar region is required to assess tumor size, localization and invasiveness and supplemented with a contrast test, if there is no objection to it. Early diagnosis of acromegaly influences not only greater success of the treatment, but also reduces complications of the disease and these have a direct impact on the quality and length of life. Therefore, one should actively look out for the disease, particularly in males and individuals suffering from cardiovascular and osteoarticular disorders that are not age-specific[5]. Our patient had symptoms for 5-6 years and was diagnosed one year after starting treatment for hypertension. Which resulted in the development of complications such as insulin resistance, arterial hypertension, atherogenic dyslipidemia, asymptomatic sinus bradycardia, second degree mitral valve regurgitation, left ventricular enlargement. Laboratory tests showed remarkably high values of GH- 171.400 ng/ml and IGF-1- >1600.0 ng/l and secondary low values of testosterone- 90.39 ng/dl. The MRI performed a lesion of the pituitary macroadenoma with dimensions 25x20x24mm.

When selecting a treatment option, one should assess possible complications as well as the patient's health status and preferences. The treatment of choice that may achieve cure involves selective surgical removal of pituitary adenoma, using a transsphenoidal approach if feasible, while hormonal function of the residual gland is preserved. As most tumors at the diagnosis of acromegaly are macroadenomas, surgical treatment is effective (GH concentration <1.0 µg / l) only in 30% -50%, in contrast to microadenomas, where surgical success is achieved in approximately 70-90% of patients[11]. In the case of our patient with pituitary macroadenoma, the surgery did not cure it, but only decreased GH and IGF-1 values and reduced symptoms.

Patients with active acromegaly, after unsuccessful surgery for pituitary adenoma or awaiting the effects of radiotherapy, should receive long-acting somatostatin analogues at doses that ensure normalisation of the GH and IGF-1 levels[6]. The first-generation SRLs have high affinity for somatostatin receptors SSTR2 and weak to moderate affinity for SSTR3 and SSTR5. There are no significant differences in the effectiveness and tolerability between Lanreotide Autogel and Octreotide LAR. Actually, without the use of stringent inclusion criteria required for clinical trials, in unselected treatment-naïve acromegalic patients a biochemical control can be achieved in a percentage which is far lower than those reported in the past, while real life studies indicate a biochemical control rate around 40%[4]. The poor response to Lanreotide Autogel as a therapy was probably expected because of the biochemical resistance already shown to Lanreotide Autogel

and Octreotide LAR before surgery. This patient had many determinants of a poor response, such as young age, sex, tumor volume, high baseline hormonal levels and sparsely granulated adenoma and these parameters probably should have led us to anticipate other therapeutic decisions.

The switch to PEG as a monotherapy or in association with SRLs represents a valid strategy in resistant patients[1]. Biochemical control was achieved during PEG therapy, the GH and IGF-1 secretion was normalised. The patient experienced no side effects during PEG therapy, unlike the SRLs therapy, where higher bilirubin values were reported. An additional advantage was the reduction of signs and symptoms, in particular the reduction of body weight. Nevertheless, the use of PEG has some practical limitations, such as dosage and route of administration (everyday injections) and its high cost, when compared with somatostatin analogs[12]. It is worth noting that this treatment with PEG, which must be practiced until the rest of this young patient's life, is very expensive and the health economics issue and the cost effectiveness of different treatments are important considerations in management decisions in acromegaly.

**Conclusions:** Treatment with pegvisomant is now an important therapeutic strategy to achieve full disease control in acromegalic patients resistant or poorly responders to first generation somatostatin receptor ligands and in patients who do not respond adequately to selective excision of pituitary adenoma and /or for whom surgery is not possible.

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