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The place of medical treatment of acromegaly in Serbia: current status

Mesto medikamentne terapije akromegalije u Srbiji – aktuelno stanje

Mirjana Doknić, Marko Stojanović

University of Belgrade, Faculty of Medicine, Belgrade, Serbia; Clinical Center of Serbia, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia

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Ključne reči:
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Introduction

Acromegaly is a chronic, multisystemic disease, caused in 98% of cases by a somatotroph pituitary adenoma [1, 2]. Secretory hyperactivity of somatotroph adenoma results in the abnormal serum concentration of growth hormone (GH) which either directly, or more often through its physiological mediator – insulin like growth factor-I (IGF-1), causes the spectrum of complications of this disease. The prevalence of acromegaly in Europe is estimated to 28–137 cases per million, and the estimation of annual incidence varies from 2 to 11 patients per million [3, 4]. Due to its slow onset and insidious progression, acromegaly often remains long unrecognized in spite of presence of signs and symptoms. Time from first symptoms to diagnosis is estimated as 5–10 years [2, 5]. Acromegaly caused by diseases other than somatotropinoma is exceptional. These rare cases include ectopic GH or GH-releasing hormone (GHRH) secretion from lung, pancreas, adrenal or mediastinal tumors [6]. Over the past 20 years, genetic background has been elucidated for some forms of acromegaly, occurring syndromicaly within MEN 1, MEN 4, McCune Albright or Carney complex or as part of isolated familial pituitary adenoma (FIPA) [7, 8].

Along the hallmark signs and symptoms of acromegaly, such as enlargement of hands, feet, nose and ears, facial soft tissue swelling or mandible protrusion, the most frequent complications of the disease are: diabetes mellitus, arterial hypertension, cardiovascular diseases (heart failure, arrhythmias, atherosclerosis, endothelial dysfunction), articular deformities in large joints, vertebral fractures (with or without osteoporosis), respiratory disfunction (obstructive sleep apnea syndrome) and thyroid, colon or prostate neoplasia [1, 9–14]. Patients with active acromegaly are attributed with a 2 to 3-fold increase in mortality rate compared to general population. The average life expectancy in these patients is reduced by an average of 10 years compared to healthy controls. The leading causes of death in this group are malignancies, cardiovascular and respiratory diseases [15]. An adequate control of acromegaly enables prevention or attenuation of the disease complications and converging of the mortality rate of these patients to the one in general population [4, 16].

The goals in acromegaly treatment are: normalization of serum IGF-1 (for the age specific reference range), achieving serum GH < 1 μg/L, reduction of pituitary tumor mass or its GH-secreting remnant, elimination or reduction of disease symptoms and comorbidities [17, 18]. The treatment of acromegaly includes a combination of several modalities: neurosurgical operation, medical treatment and radiotherapy. Over the last two decades a significant advancement was made in the field of acromegaly medications development, promoting a dramatical improvement in the treatment outcomes in acromegaly. Along with the contemporary internationally accepted guidelines for acromegaly treatment [19, 20], all of the aforesaid treatment modalities are in use in the Republic of Serbia. The emerging availability of novel medical options in Serbia, raises the need for generating recommendations for the place and role of each specific treatment option. Treating acromegaly is a multidisciplinary task. The key decisions should be made by an interdisciplinary team including a neuroendocrinologist, neurosurgeon, pathologist, radiologist and geneticist as needed.

Correspondence to: Mirjana Doknić, Clinical Center of Serbia, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Dr Subotića 13, 11 000 Belgrade, Serbia. E-mail: mirjanadoknic@gmail.com

Surgical treatment

Operation of GH secreting pituitary tumor represents the first line of treatment of acromegaly both worldwide and in Serbia. Somatotropinomas are operated by transsphenoidal approach in more than 90% of cases. Operative outcome is primarily dependent on the experience and skill of neurosurgeon, and on size and propagation of the tumor. A neurosurgeon is recognized as an expert in pituitary surgery if performing more than 200 transsphenoidal pituitary surgeries annually [21]. The surgical remission of acromegaly is usually defined by age-related normal IGF-1 and a random serum GH, or OGTT-nadir GH of < 1 μg/L – assessed 3 months postoperatively. In specialized pituitary neurosurgery units, remission is achieved in 75%–90% of microadenomas and 45%–70% of macroadenomas [22]. Repeated pituitary surgery should be considered in consensus of all members of pituitary multidisciplinary expert team involved in the treatment of patient. Decision on reoperation is based on disease activity, size and location of tumor remnant, optic chiasm compromisation, and the response to medical treatment. Remission achievement after the second operation is reported in about one half of cases [23].

Medical treatment

Since overall in about 60% of acromegaly patients biochemical control of disease is not achieved by operation, the care is continued by medical therapy which represent the second line of treatment [7, 20]. Medical treatment of acromegaly encompasses three groups of drugs: 1) somatostatin receptor ligands of 1st generation (SRL-fg): [octreotide long-acting release (LAR) and lanreotide autogel] or 2nd generation (pasireotide LAR); 2) dopamine agonists – DA (bromocriptine, cabergoline) and 3) GH-receptor antagonists (pegvisomant) (Figure 1).

Somatostatin receptor ligands – first generation

Somatostatin receptor ligands of 1st generation, which are in use in Serbia for treatment of acromegaly are octreotide LAR and lanreotide autogel. These drugs consist the first line of medical treatment and are approved for treatment of acromegaly since 2004. [7]. These are synthetic long acting agonists of somatostatin receptor, with high affinity for subtype 2 of somatostatin receptor (SSTR-2) and a lesser affinity for subtype 5 of somatostatin receptor (SSTR-5). Availa-

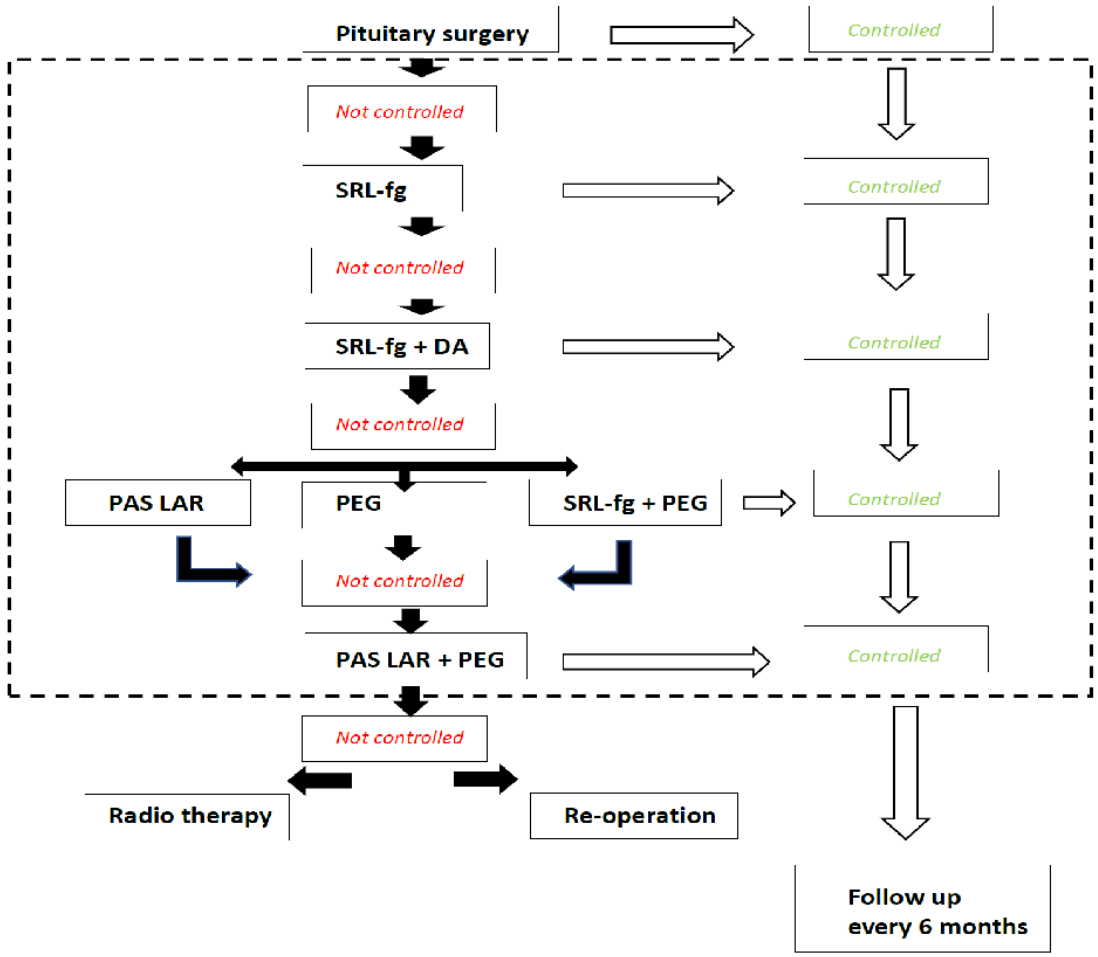

Fig. 1 – Recommended decision sequence in medical treatment of acromegaly and its place within acromegaly multimodal treatment algorithm.
PAS LAR – pasireotide long-acting release; SRL-fg – somatostatin receptor ligands of first generation; DA – dopamine agonists; PEG – pegvisomant.

ble drugs and doses in Serbia include octreotide LAR (20 mg and 30 mg) and lanreotide autogel (90 mg and 120 mg), both applied once in 28 days as an intramuscular injection and subcutaneous injection, respectively. The latest recommendation, also observed in Serbia, advises a maximal initial dose of these medications (octreotide LAR 30 mg or lanreotide LAR 120 mg) over the first 6 months of treatment, followed by optional dose reduction or an increase in dosing intervals (e.g. lanreotide autogel once in 56 days, instead of 28 days) after the achievement of biochemical disease control [24]. The first control of GH and IGF-1 is scheduled for 3 months after the SRL-fg treatment initiation. In the case of inefficiency of one of the drugs from this group, the switch to the other SRL-fg should be tried [25]. Overall, no superiority in efficacy was established for one of SRL-fg over the other [26]. These drugs effectively inhibit GH synthesis and somatotroph cells proliferation, thus inducing reduction in tumor size. A complete biochemical response to SRL-fg is defined by serum GH of < 1 μg/L and IGF1 normalization, and it is achieved in 30% of treated patients. A partial response is defined by a reduction in GH and/or IGF-1 for ≥ 50% from baseline, and it is achieved in 50% of patients. Resistance to SRL-fg is characterized by a decrease in serum GH and IGF1 for < 50% from baseline, and it is observed in 20% of patients [27]. Decrease in tumor remnant size for > 20% is observed in 65% of patients treated with SRL-fg. Reduction of tumor size is expected after 6 months of treatment [28]. SRL-fg treatment is generally well tolerated and these drugs are believed to have a good safety profile. Side effects of these drugs are mostly associated with gastrointestinal impairment (nausea, abdominal pain, diarrhea, gall bladder stones or sludge, constipation, malabsorption, liver function derangements) [29]. Cholelithiasis occurs in about 30% of patients treated with SRL-fg, usually in the first two years of treatment, rarely demanding cholecystectomy. Glucose tolerance impairment is observed in about 30% of patients, while in less than 5% either bradycardia, hypertension or anemia are reported [30]. Dose reduction usually leads to resolution of side effects.

Indications for SRL-fg treatment include conditions when: remission of acromegaly was not achieved by surgery; somatotroph adenoma with extensive propagation into cavernous sinuses makes the expectance of surgical effect unlikely; lack of effect of radiotherapy (as assessed 5 to 10 years after stereotactic treatment).

Pasireotide LAR

SRL of second generation (SRL-sg), pasireotide LAR, represents the second line of medical treatment in acromegaly, reserved for patients which partially respond to SRL-fg (Figure 1). This drug received approval for treatment of acromegaly in 2014 by European Medicine Agency (EMA) and Food and Drug Administration (FDA) [7]. Pasireotide LAR is a multireceptor somatostatin ligand with the highest affinity for somatostatin receptor subtype SSTR-5, followed by the SSTR-1, and with a lesser affinity for SSTR-2 in comparison to the SRL-fg (octreotide and lanreotide). Owing to the greater number of the receptors to which it binds, pasireotide LAR assures a better clinical effect compared to SRL-fg. Results of clinical studies involving this drug demonstrate IGF-1 normalization in 20% of patients resistant to SRL-fg treatment [31]. Pasireotide LAR also exhibits a better antitumor effect compared to SRL-fg, reducing the tumor size by 40% in about 80% of treated patients. All these characteristics make pasireotide LAR the drug of choice for acromegaly patients with a tumor remnant in proximity to optic chiasm [32]. Pasireotide LAR is available world wide in doses of 10 mg, 20 mg, 30 mg, 40 mg and 60 mg, applied as an *im* dose once in 4 weeks. In Serbia, pasireotide LAR is currently available in the 40 mg dose, which is the initial dose for treatment, while 60 mg is the maximal monthly dose of this drug.

The treatment with pasireotide LAR is considered in the following cases: unsuccessful SRL-fg treatment in an acromegaly patient with a tumor remnant of considerable size; in patients younger than 40 years in whom a growth of tumor remnant is observed while they are on SRL-fg treatment, and the tumor is unsuitable for surgical treatment (clinically aggressive tumor); in patients with severe headaches, not controllable by SRL-fg treatment; in patients not responding or not tolerating pegvisomant treatment. The side effects profile of pasireotide LAR is similar to that of SRL-fg, except for glycemic impairment, which is observed in around 70% of treated patients [33]. In about 10% of patients, pasireotide LAR treatment needs to be discontinued due to hyperglycemia. In the first 3 months after treatment initiation, fasting glucose evaluation is advised once weekly, and afterwards once in 6 weeks. In the treatment of diabetes mellitus induced by pasireotide LAR application, metformin is used and additionally if needed, dipeptidyl peptidase-4 inhibitors (DPP4), glucagon-like peptide-1 (GLP-1) receptor agonists, while insulin treatment is reserved for the most severe derangements [34]. In the case of overt diabetes mellitus occurring while on pasireotide LAR treatment, these patients could be considered for further treatment with pegvisomant (Figure 1). Pasireotide LAR may suppress anterior pituitary hormone secretion, and treated patients should be under surveillance for development of hypopituitarism.

Dopamine agonists

Dopamine agonists (DA) currently used in Serbia for acromegaly treatment are bromocriptine and cabergoline. DA are used as a first and second line medical treatment, usually in combination with SRL-fg, pasireotide LAR or pegvisomant [20]. Cabergoline is attributed with a greater efficacy in remission achievement in acromegaly (estimated as 34%) compared to bromocriptine (10%) [35]. Mechanism of action of DA in acromegaly relies on the fact that most somatotroph adenomas exhibit type 2 dopamine receptors (D2R), and about 20% of these tumors, in addition to GH co-secrete prolactin (mixed somatotroph/lactotroph tumors). The efficacy of DA is limited to milder forms of

disease, but oral application and low cost make them nevertheless attractive for treatment in acromegaly [36]. The average dose of cabergoline is 2.5 mg weekly (ranging from 1 to 7 mg) which is 2 to 5-fold greater than the doses used in hyperprolactinemia.

Dopamine agonists are used in treatment of acromegaly in following cases (Figure 1): mild biochemical activity of acromegaly (IGF-1 < 2.5 ULN – upper limit of normal for age) with mild disease symptoms. The optimal effect of DA is achieved in cases with IGF-1 < 1.5 ULN; mixed somatotroph/lactotroph pituitary adenoma, prior to surgery, or if remission is not achieved by surgery; as add-on treatment in patients partially responding to SRL-fg.

Pegvisomant

Pegvisomant is a pegylated recombinant GH analogue, acting as a selective antagonist of GH-receptor (GHR). It is used as a second line medical treatment of acromegaly [7, 20]. Pegvisomant was registered in EU in 2002 (EMA approval) and in USA in 2003 (FDA approval) for treating patients with acromegaly [7]. By competing for the GHR, pegvisomant blocks the binding of GH to its receptor, hence preventing the action of GH. The objective of pegvisomant treatment is normalization of serum IGF-1 level. Considering that pegvisomant does not reduce GH concentration, the effects of treatment can only be followed by analysis of serum IGF-1. Serum IGF-1 normalization is reported in about 65% of patients treated with pegvisomant for 5 years [37]. Pegvisomant is available in doses of 10 mg, 15 mg, 20 mg, 25 mg and 30 mg, for subcutaneous (*sc*) injection once daily. Initial daily dose of the drug is 10 mg, and the maximal dose is 30 mg daily [14]. Treatment dose of pegvisomant needs to be titrated individually. An increase or decrease by a 5 mg in daily dose is advised, until IGF-1 normalization is achieved. Pegvisomant decreases levels of glucose and HbA1c, thus enabling reduction in doses of insulin or oral antidiabetic agents in acromegalic patients with diabetes mellitus [38].

Pegvisomant is recommended in following cases: acromegalic patients treated with SLR-fg with persistent disease but small or undetectable tumor remnant; acromegalic patients uncontrolled on SRL-fg, who also suffer from diabetes mellitus; acromegalic patients developing diabetes mellitus in the course of treatment with pasireotide LAR.

Higher doses of pegvisomant are used in female patients, younger, and those with a higher IGF-1 concentration, as well as in patients with diabetes mellitus, sleep apnea syndrome, and in patients with higher body mass index [39]. Although mainly used once daily, pegvisomant may be used twice weekly or once weekly, alone or in combination with other medical modalities for treatment of acromegaly (e.g. SRL-fg). Pegvisomant acts on extrahepatic (IGF-1 independent) GH effects, thus being useful even in patients in whom IGF-1 normalization was already achieved by other modalities of acromegaly treatment (e.g. SRL-fg). In these patients, small doses of pegvisomant, applied once or twice weekly, may relieve the patient of edema, headaches or fatigue, thus significantly improving the quality of life [40]. Pegvisomant found its place also in patients with familial form of acromegaly (aryl hydrocarbon receptor-interacting protein - AIP mutation positive patients). These are often young patients, with progressive course of disease, invasive pituitary tumors and poor response to SRL [8, 41]. Patients suffering from acromegaly as a manifestation of McCune Albright syndrome exhibit resistance to SRL and a favorable response to pegvisomant [42].

Pegvisomant is generally a safe drug which is well tolerated, in spite of the fact that it is administered daily as *sc* injection. Side effects are not dose dependent, and are usually transient and do not require additional treatment. The largest study of efficacy and safety of pegvisomant treatment, (ACROSTUDY) with 2,090 patients followed for 7.6 years, reported the following side effects: headache (in 4.9%), arthralgia (in 3.7%), erythema or other local skin reactions to drug application (in 3.1%), lipodystrophy or lipo-hypertrophy (in 1.7%), gastrointestinal disturbances (in 1.2%) and elevated liver enzymes (in 3%) [43]. Impairment of liver function tests is reversible upon dose reduction or drug discontinuation. Drug discontinuation is advised if the level of liver enzymes is 5-fold above upper limit of normal (0.5%). Due to the known possible elevation of liver enzymes, follow up of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) is advised every 4–6 weeks in the first 6 months of treatment. To avoid potential local skin reactions to drug application, sites of administration should regularly be altered. Pegvisomant has no effect on pituitary tumor remnant size reduction, and is even attributed with a small potential risk of its increase (in 1–3%) [44]. Treatment with pegvisomant is thus not recommended if the tumor remnant is larger or if its distance from the optic chiasm is less than 3 mm [19]. Follow up sellar region MRI is advised during pegvisomant treatment.

Preoperative medical treatment

Medical treatment in acromegaly could also be considered preoperatively, as the first line of treatment (mainly involving SRL-fg), resulting in an increased rate of biochemical disease control, compared to patients operated without prior medical treatment. However, current literature does not provide sufficient evidence to justify a benefit of preoperative treatment with SRL-fg [45].

Conditions in which medical therapy is the first line of treatment in acromegaly include: contraindications for surgery; need for preoperative reduction in surgical and anesthetic risk in acromegaly complicated by: high output cardiac failure, severe pharyngeal thickness and swelling of soft tissue, or severe sleep apnea syndrome.

Combined medical treatment

Combined medical treatment is advised when monotherapy with SRL-fg is insufficiently effective (Figure 1).

Addition of cabergoline to SRL-fg treatment enables IGF-1 normalization in over 50% of patients uncontrolled by SRL-fg monotherapy [46]. Combination of cabergoline and pegvisomant may be an effective alternative in patients not responding to SRL-fg treatment [47]. IGF-1 normalization is expected in 34% of patients when cabergoline is used as monotherapy, and in up to 68% of patients on combined cabergoline and pegvisomant treatment. If this combination is also ineffective, it is advised to consider the combined treatment of SRL-fg and pegvisomant, which was observed to provide better results in patients uncontrolled by monotherapy with either of the drugs (Figure 1). This combination acts both on normalization of IGF-1 serum level and reduction of tumor remnant size. It was reported to provide IGF-1 serum level normalization in 60–97% of patients while reduction in tumor remnant size is expected in 20% of patients [35, 48]. Combined use of SRL-fg and pegvisomant enables dose reduction for both drugs, possibly decreasing treatment costs. If biochemical control is not achieved with this combination of drugs, or an increase is observed in tumor remnant size, it is advised to consider the combined treatment with pasireotide LAR and pegvisomant [20, 49].

Currently, pasireotide LAR and pegvisomant are available in Serbia under a specific clinical programme.

Other medical treatment

When acromegaly persists despite of all the abovementioned treatment modalities, temozolomide may be considered. This drug is an alkylating agent used in treating advanced aggressive neuroendocrine tumors and pituitary carcinomas [50]. Reports on the efficacy of this drug in treatment of acromegaly are limited, indicating efficacy in about 50% of patients [35].

Radiotherapy

This therapeutic modality represents the third line of treatment in acromegaly, to be considered in patients with aggressive pituitary tumors, resistant to surgical or medical treatment [7, 20]. Stereotactic radiosurgery (SRT) is superior to conventional radiotherapy in efficacy and safety. During SRT treatment, high radiation doses are delivered directly to tumor tissue, largely sparing the neighboring healthy tissue. Radiotherapy is mostly reserved for aggressive tumors. Tumor size control is achieved in over 90% of patients, biochemical control in about 60% of patients, but the full effect of treatment is only expected after 5-10 years from SRT application [51]. Major side effect of radiotherapy is hypopituitarism, observed in 70% of treated patients, while optic nerve lesions, cerebrovascular impairment or secondary tumorigenesis are much less frequent [52]. SRT is not recommended when tumor is in high proximity to optic chiasm. SRT modalities available in Serbia include “gamma knife” and “X knife”. Prior medical treatment of acromegaly (with SRL or DA) is believed to be associated with a possible reduction in radio-sensitivity. A temporary cessation of medical treatment, although not an universally recommended practice, was observed to improve both initial and long-term effect of SRT. SRL are advised to be discontinued 6 to 8 weeks prior of SRT and restarted 4 to 8 weeks after, while DA can be discontinued only 2 weeks before SRT. Pegvisomant, as a drug not targeting the pituitary tumor, should not influence radio-sensitivity and does not need to be discontinued [52].

Radiotherapy should be considered in following cases: tumor remnant and active acromegaly are persistent after somatotroph adenoma surgery followed by multimodal medical treatment (SRL-fg, DA, SRL-sg, pegvisomant); medical treatment is ineffective, unavailable, or needs to be discontinued due to side effects.

Personalized approach to patient and prognostic factors of outcome

Judging by the international registries data, one third of acromegaly patients are undertreated and lack disease control [3]. Considerable cost of some medications used in treatment of acromegaly (pasireotide LAR, pegvisomant), result in their unavailability, particularly in the countries of eastern and central Europe [53]. In the course of treatment of acromegaly, in addition to follow up of GH and IGF-1 serum levels, and tumor remnant size, evaluation of patient`s quality of life is recommended, through the use of AcroQoL questionnaire, as well as disease activity clinical assessment with the use of Acromegaly Disease Activity (ACRODAT) or Signs and Symptoms (SAGIT), Associated Comorbidities, GH levels, IGF1 level, and Tumor Profile questionnaires [54–56].

In more than 50% of acromegaly patients, application of all treatment modalities is necessary. Every patient demands individual approach in selection of optimal treatment modalities or their combinations [3, 57]. Personalized approach to patients with acromegaly is founded on the understanding of prognostic factors, on which the individualized selection of treatment is based upon. The optimal selection of treatment includes not only the wellbeing of the patients, but also the most economical approach to the public funding resources. Predictive factors for treatment outcomes include patient`s clinical characteristics – age, gender, the size of pituitary tumor or tumor remnant, baseline GH and IGF-1 levels, histological and immunohistochemical characteristics of the operated tumor tissue, tumor expression of somatostatin receptors, tumor signal intensity on magnetic resonance imaging (MRI) and possible genetic background of acromegaly including FIPA, MEN-1 syndrome, G-protein-linked receptor mutation – *gsp* oncogene mutation, McCune Albright syndrome, X-linked acrogigantism [58].

Female gender, younger age, larger tumor size and high initial GH levels are general indicators of poor response to treatment, and a poor prognosis of the disease. Patients expected to respond better to SRL-fg are those with: tumor hypointensity in T2w MRI, densely granulated tumor tissue, lower Ki67 proliferative index and higher tumor expression of SSTR2A. A favorable response to pasireotide LAR treat-

ment is expected in patients with higher SSTR5 expression in tumor tissue, although SSTR2A expression is also a predictor of good response [57]. Better prognosis after pegvisomant treatment is anticipated in male patients, prior radiotherapy, and in some of GH receptor gene polymorphisms (lack of d3-RHR). AIP mutation positive patients and patients with McCune Albright syndrome are frequently resistant to SRL, thus making pegvisomant the drug of choice in these groups [58]. On the contrary, *gsp* mutation positive patients are excellent responders to SRL [59] (Table 1).

Conclusion

In spite of significant advancement in discovery of new biomarkers as possible prognostic factors in selection of medical treatment of acromegaly, their value has not been demonstrated in clinical practice. The response to treatment in acromegaly can not be predicted with certainty, despite of the various mentioned prognostic factors. Adequate multimodal treatment of acromegaly enables remission of the disease in almost all patients.

Table 1

Predictors for treatment response to medical therapy in acromegaly

Predictors	SRL-fg	SRL-sg	Pegvisomant
Clinical			
female gender	↓		
male gender			↑
younger age	↓		
larger tumor size	↓		
high initial GH levels	↓		
prior radio-therapy			↑
Radiological			
tumor hypo-intensity in T2w MRI	↑		
Pathological			
densely granulated tumor tissue	↑		
lower Ki67 proliferative index	↑		
higher tumor expression of SSTR2A	↑		
higher tumor expression of SSTR5		↑	
Genetic			
AIP mutation positive	↓		↑
McCune Albright syndrome	↓		↑
gsp mutation	↑		
GH-receptor gene polymorphism			↑

↑ = positive; ↓ = negative; SSTR – somatostatin receptor; SRL-fg – somatostatin receptor ligand-first generation; SRL-sg – somatostatin receptor ligand-second generation; GH – growth hormone; AIP – aryl hydrocarbon receptor-interacting protein; MRI – magnetic resonance imaging.

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