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POSITION STATEMENT

Italian Association of Clinical Endocrinologists (AME) and Italian AACE Chapter Position Statement for Clinical Practice: Acromegaly - Part 2: Therapeutic Issues

Renato Cozzi[1,*], Maria R. Ambrosio[2], Roberto Attanasio[3], Alessandro Bozzao[4], Laura De Marinis[5], Ernesto De Menis[6], Edoardo Guastamacchia[7], Andrea Lania[8], Giovanni Lasio[9], Francesco Logoluso[10], Pietro Maffei[11], Maurizio Poggi[12], Vincenzo Toscano[12], Michele Zini[13], Philippe Chanson[14] and Laurence Katznelson[15]

[1]Division of Endocrinology, Niguarda Hospital, Milan, Italy; [2]Section of Endocrinology and Internal Medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [3]Endocrinology Service, IRCCS Orthopedic Institute Galeazzi, Milan, Italy; [4]Neuroradiology, S. Andrea Hospital, NESMOS Department (Neuroscience, Mental Health, Sensorial Organs), Sapienza University of Rome, Rome, Italy; [5]Pituitary Unit, Department of Endocrinology, Catholic University of the Sacred Heart, School of Medicine, Rome, Italy; [6]Department of Internal Medicine, General Hospital, Montebelluna (TV), Italy; [7]AME President, University of Bari, Bari, Italy; [8]Department of Biomedical Sciences, IRCCS Humanitas University and Endocrinology Unit, Humanitas Research Hospital, Rozzano, Italy; [9]Department of Neurosurgery, Humanitas University and Endocrinology Unit, Humanitas Research Hospital, Rozzano, Italy; [10]Endocrinology Unit, Department of Emergency and Organ Transplantation, University Medical School 'Aldo Moro', Bari, Italy; [11]Department of Medicine (DIMED), 3rd Medical Clinic, Padua University Hospital, Padua, Italy; [12]Endocrinology, Department of Clinical and Molecular Medicine, S. Andrea Hospital, Sapienza University of Rome, Rome, Italy; [13]Endocrinology Unit, Azienda Ospedaliera S. Maria Nuova IRCCS, Reggio Emilia, Italy; (All on behalf of AME and AACE Italian Chapter[1]);[14]Endocrinology and Reproductive Diseases, Bicêtre Hospital and Paris-Saclay University 11, France; [15]Department of Medicine, Stanford University Hospital, Stanford, CA, USA

Abstract: Any newly diagnosed patient should be referred to a multidisciplinary team experienced in the treatment of pituitary adenomas. The therapeutic management of acromegaly always requires a personalized strategy. Normal age-matched IGF-I values are the treatment goal. Transsphenoidal surgery by an expert neurosurgeon is the primary treatment modality for most patients, especially if there are neurological complications. In patients with poor clinical conditions or who refuse surgery, primary medical treatment should be offered, firstly with somatostatin analogs (SSAs). In patients who do not reach hormonal targets with first-generation depot SSAs, a second pharmacological option with pasireotide LAR or pegvisomant (alone or combined with SSA) should be offered. Irradiation could be proposed to patients with surgical remnants who would like to be free from long-term medical therapies or those with persistent disease activity or tumor growth despite surgery or medical therapy. Since the therapeutic tools available enable therapeutic targets to be achieved in most cases, the challenge is to focus more on the quality of life.

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*Address correspondence to this author at the Endocrinologia, ASST Grande Ospedale Metropolitano Niguarda, Piazza Ospedale Maggiore 3, 20162 Milano, Italy; Tel: +39.347.5225490; E-mail: dr.renatocozzi@gmail.com

This document reflects the state of the art at the time of publication and it aims to standardize clinical practice. We encourage medical professionals to always use this information in conjunction with their best clinical judgment, as the presented recommendations may not be appropriate in all situations. Any decision by practitioners must be made in light of local resources and individual patient circumstances.

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This document follows and completes a previous version of the manuscript (Cozzi, R.; Ambrosio, M.R.; Attanasio, R.; Bozzao, A.; De Marinis, L.; De Menis, E.; Guastamacchia, E.; Lania, A.; Lasio, G.; Logoluso, F.; Maffei, P.; Poggi, M.; Toscano, V.; Zini, M.; Chanson, P.; Katznelson, L. Italian Association of Clinical Endocrinologists (AME) and Italian AACE Chapter Position Statement for Clinical Practice: Acromegaly - Part 1: Diagnostic and Clinical Issues. Endocr Metab Immune Disord Drug Targets, 2020, PMID: 31985386 DOI: 10.2174/1871530320666200127103320 [Epub Ahead of Print]) addressing the diagnostic and clinical issues of acromegaly (the listing of paragraphs is thus the continuation of the previous document)

5. THERAPEUTIC ISSUES

5.1. Aims of Treatment

The ideal treatment should be able to quickly control hormonal hypersecretion by normalizing growth hormone (GH) and insulin-like growth factor (IGF)-I levels, remove tumor as well as signs and symptoms of the disease, reverse comorbidities, reduce mortality to that of control population, and improve quality of life (QoL). Although the results of current treatments represent outstanding progress compared to those achieved a few decades ago, they are still not always ideal.

Every newly-diagnosed patient should be referred to a multidisciplinary team experienced in the treatment of pituitary adenomas (including endocrinologists, neuroradiologists, neurosurgeons, radiotherapists/radiosurgeons) [1].

5.2. Neurosurgery

Transsphenoidal surgery (TSS), using a microscopic or endoscopic technique, is the procedure of choice, whenever applicable [2, 3]. The success rate is mainly affected by the tumor invasivity, followed by preoperative GH levels and the surgeon's expertise [4-7]. The reported remission rates after TSS performed by high-volume pituitary surgeons in the most recent publications are up to 75% for non-invasive macroadenomas, and up to 85% for microadenomas [8-10]. Cavernous sinus invasion is generally associated with a rate of remission of up to 40% [8, 11], which drops to 0 in cases with Knosp grade 4 invasion. The success rate in the real world, *i.e*. according to data reported by registries, thus combining results of surgeons with different expertise, is much lower (ranging 20-37%) [12]. The need to refer patients to high volume centers is clear from these data.

Patients who should undergo surgical intervention as a first-line therapy are those for whom surgery is expected to cure the disease (*i.e*. patients with non-invasive both micro and macro tumors) and those who require an immediate resolution of neurological symptoms (*i.e*. local mass effects on the optic chiasm).

Although not widely available, morphological and molecular analyses performed on surgical samples could be used as a guide for the following treatments.

It has been suggested that pre-surgical SSA treatment might favor a radical resection of the tumor [13]. However, current data do not support the routine use of presurgical medical therapy [2, 13-20]. Conversely, for patients with severe respiratory and/or cardiovascular complications due to acromegaly, pre-operative medical treatment can be considered in order to reduce perioperative morbidity [2, 13], although contrasting data have been reported [21].

Surgical debulking should be considered in patients with invasive adenomas that are fully resistant or partially responding to somatostatin analogs (SSAs). In this latter event, the procedure results in a better response to postoperative SSA treatment and can provide tissue for pathological analysis [2, 22, 23].

Operative mortality approaches zero, and morbidity related to TSS operations is mainly represented by transient diabetes insipidus (8%) and cerebrospinal fluid leaks requiring reoperation (3%). Pituitary secretion of other hormones is damaged in 6% of patients [24].

In the case of a large persistent/recurrent tumor inside the sella that is resistant to the pharmacological treatments available, a new TSS operation is a valuable option, although side effects are slightly more frequent [25-27].

When a residual tumor is present in the cavernous sinus, focused beam radiosurgery is also a valuable option (see 5.4).

We recommend referral to an experienced neurosurgical team.

We recommend surgery as the first-line therapy if a) the adenoma is totally resectable and biochemical remission is predictable or b) the pituitary adenoma is associated with a mass effect, especially visual field impairment.

We suggest debulking surgery in patients with resistance to medical treatments.

5.3. Pharmacological Treatments

5.3.1. Monotherapies

5.3.1.1. First-Generation SSAs

Octreotide and lanreotide inhibit effectively hormonal hypersecretion in most patients, achieving normal (or near normal) IGF-I levels in nearly 50% of cases [28-30], without tachyphylaxis, even after many years [31].

It is now commonly accepted that there is no real difference in the response to lanreotide and octreotide, although switching the two molecules may be beneficial in some patients with adverse effects [32, 33].

Control rates within post-surgery cohorts did not differ significantly from those in corresponding de-novo cohorts [34].

Clinical improvement parallels hormonal control: clinical symptoms as well as systemic comorbidities markedly improve or disappear [35-38].

Tumor shrinkage occurs in most patients [39, 40], above all in the first months of treatment, and it may be quick, and progressive [41]. The occurrence and degree of shrinkage are greater when SSAs are used as the primary treatment [40, 42, 43].

The age and sex of the patient do not influence the response to SSA treatment, whereas contrasting results regarding the role of high GH levels have been reported [41, 44, 45].

It was recently reported that hormone suppression and tumor shrinkage during SSA treatment are greater in patients with adenomatous T2 hypointensity at MRI [46-49].

The following features will be available only after surgery if an advanced workup is available. The granulation pattern at the ultrastructural examination of the resected adenoma, namely sparse or dense, helps differentiate between patients with a low or high likelihood of response to SSAs, respectively [50]. The expression of somatostatin subtype receptor (SSTR) -2 in the adenoma could be a useful tool to identify those patients who will be most likely responders to therapy with SSAs [51, 52].

In very sensitive patients, the interval between injections can be safely lengthened, thus increasing compliance and cutting costs [53].

In partially resistant patients, up-titration can obtain a better GH/IGF-I control. For octreotide LAR, this was reported by increasing the dosage but not by shortening the interval between injections [54]. For lanreotide ATG both "high-frequency" (120 mg/21 days) and "high-dose" (180 mg/28 days) regimens were effective in some patients [55].

The withdrawal of SSA treatments even after many years of tight control was followed by a relapse of hypersecretion except for anecdotal reports [56].

The net effects on carbohydrate metabolism are widely variable, but are seldom of a clinical significance [57, 58]. Diabetes mellitus occurs or worsens mostly in SSA-resistant patients or in those with family susceptibility. A recent meta-analysis evaluating the effect of SSAs on glucose metabolism parameters [59] concluded that post-prandial glucose was the most commonly involved parameter during SSA treatment; it should thus be the target of specific drugs such as incretins [60]. Aggressive anti-diabetic treatments are not usually required in patients developing minimal derangement of glucose metabolism on chronic SSA treatment.

5.3.1.2. Second Generation SSA

Pasireotide is a multi-ligand SSA that activates SSTR5, SSTR2, SSTR1, and SSTR3 with different affinities [61].

After a few preclinical and open studies [62-64], a multicentric prospective randomized head-to-head study demonstrated that pasireotide LAR was more effective than octreotide LAR in controlling hormonal hypersecretion [65]. The study raised sensation because the results obtained on pasireotide LAR were similar to those commonly reported with first-generation SSA, whereas the results of octreotide LAR were definitely worse.

In the following PAOLA study [66] patients partially sensitive to first-generation SSA at maximal doses were randomized to pasireotide LAR vs. the continuation of previous treatments. Pasireotide LAR was considerably better than previous treatments, with results persisting for up to 24 months [67, 68]. Also in a real-life scenario, a recent retrospective study by Shimon *et al.* [69] showed IGF-I normalization in 19 out of 35 patients inadequately controlled by octreotide. Interestingly, patients suffering from acromegaly headache reported a complete disappearance. Pasireotide effects on resistant headache have also been reported by other authors [70, 71]. Its use has also been recommended for headaches not responsive to first-generation SSAs in a recent position paper of the Rotterdam group [72].

The different molecular patterns of SSTRs in the adenoma, in particular of SSTR5, account for the different response to pasireotide and first-generation SSAs [73].

The side effects of pasireotide are similar to first-generation SSA, however, glucose metabolism derangement is more frequent and severe, above all in patients with pre-treatment glucose abnormalities (*i.e.* fasting plasma glucose >100 mg/dL) and/or treated with oral anti-diabetic drugs, regardless of the efficacy of the drug on acromegaly disease [74]. The optimization of anti-diabetic treatments before the start of treatment is thus mandatory together with the close monitoring of glucose values from the first weeks of therapy [75-77].

Pasireotide LAR is now authorized for acromegaly when neurosurgery is not suitable or is unsuccessful and alternative pharmacological treatments are not effective or tolerated.

5.3.1.4. Pegvisomant

Pegvisomant (PegV) is a GH receptor antagonist [78] that is authorized in Italy for acromegaly patients with the active disease after unsuccessful neurosurgery, when SSAs

are ineffective or not tolerated or while awaiting results of radiation treatments.

Disease activity on PegV treatment can only be evaluated biochemically by IGF-I levels.

In registrative studies, PegV monotherapy achieved IGF-I normalization in 63-97% of treated patients [79, 80], with a concomitant improvement in signs and symptoms including QoL.

Observational studies [81] have shown a lower success rate in clinical practice than in registrative studies, with IGF-I normalization obtained in less than 65-70% of treated patients. This feature has been attributed to inadequate up-titration of the drug.

Higher drug doses may be required in males as well as patients with diabetes mellitus, obesity or severe GH hypersecretion [81].

PegV treatment is usually associated with an improvement in glucose metabolism [81, 82]. This second-line treatment should thus be considered in patients with diabetes mellitus, above all if the metabolic disease is deranged on SSA treatment.

With regard to safety, PegV does not act on the adenoma, however, in long-term observational studies [81] tumor size was stable in most cases. A clinically significant tumor size increase has rarely been reported (nearly 3%) and has been attributed to the natural history of the adenoma or to the withdrawal of a previous treatment with SSA that had obtained tumor shrinkage [81]. On the other hand, a decrease in tumor size has been observed in a few cases. MRI surveillance is always recommended, mostly in patients with large tumor remnants and aggressive disease, who have not previously been submitted to radiation therapy.

Transient elevation in liver enzymes has been reported in <3% of patients on PegV treatment, mostly in those patients concomitantly treated with SSA.

The rotation of injection sites is recommended in order to minimize the risk of lipo-hypertrophy.

We recommend starting medical treatment with a first-generation SSA.

We suggest starting pasireotide LAR in patients who are resistant to first generation SSAs, provided that glucose metabolism is not deranged.

We recommend starting PegV in patients who are resistant or intolerant to SSA therapy after unsuccessful surgery or who are awaiting the results of radiotherapy.

We recommend early and close monitoring of glucose levels during the administration of pasireotide.

We suggest considering pasireotide for acromegaly patients with resistant headaches.

We recommend that the treatment efficacy of PegV should be monitored with IGF-I, but not GH.

We recommend regularly monitoring the tumor size, particularly in patients with large remnant and clinical aggressive disease.

We recommend monitoring liver function tests at the start of PegV treatment and during dose titration.

5.3.2. When and How to Use Combined Pharmacological Treatments

The combination of two different drugs that act either additively or synergistically may either improve efficacy or reduce the side effects associated with every single medication, decrease the frequency of injections and/or drug dose, improve compliance during long-term treatment, and possibly reduce costs related to acromegaly treatment. There are no RCTs of combined pharmacological treatments in acromegaly.

5.3.2.1. SSA + Cabergoline

Although it is still an off-label therapy for acromegaly, cabergoline monotherapy has been demonstrated to normalize IGF-I in up to 45% of selected patients (*i.e*. with a mild elevation of GH and IGF-I levels), using a dose of up to 0.5 mg/day [2, 83].

The addition of cabergoline to SSA in partially sensitive patients leads to IGF-I normalization in 30 to 45% of cases [2]. Note that baseline PRL, positive immunohistochemical staining for PRL, and D2R expression are not predictive of cabergoline addition efficacy [83-86].

5.3.2.2. SSA + PegV

Several studies have demonstrated that PegV addition (even with a 2-3 times a week schedule) leads to IGF-I normalization in 62% to 100% of patients previously considered as partially controlled on SSA [87-92]. Pasireotide LAR has also been successfully associated with PegV in small series [93, 94].

Current clinical data show that SSA and PegV can be combined in patients who partially respond to SSAs and in biochemically uncontrolled patients with a large tumor remnant.

5.3.2.3. Pegvisomant + Cabergoline

Although no conclusive data are available [95, 96], a combination of PegV and cabergoline may be considered in patients with mildly elevated IGF-I levels during PegV monotherapy, or in those with mixed GH-PRL hypersecretion [2].

We suggest combining treatments in order to improve efficacy or reduce the side effects associated with each individual medication, to decrease the frequency of injections and/or drug dose, to improve compliance and reduce costs.

Whenever a combined treatment is indicated, **we suggest** the administration of a combination with proven efficacy, *i.e*. SSA + cabergoline or SSA + PegV.

Irrespectively of the secretory status of a female acromegaly patient, oral estrogens (such as the pill in reproductive age) or selective estrogen receptor modulator treatment can decrease IGF-I levels also up to normal levels, both alone and in combination with other treatments [97].

5.4. Radiation Treatment

Irradiation can be considered in patients with still active disease after surgery. Both stereotactic fractionated radio-

therapy (FRT) and radiosurgery (RS), by gamma knife, cyberknife or proton beam, are suitable depending on the size of the residual adenoma, the proximity to optic pathways, and local availability.

The efficacy (and safety) of radiation treatment is dose-dependent, equipment-dependent, and operator-dependent. RS allows the administration of a higher dose on the target, but it requires a small remnant with a minimum gap of 2-3 mm from the optic pathways.

Endocrine remission is achieved in 50% of acromegaly patients three years after gamma knife treatment, and the percentage of cured patients 10 years after treatment is 65% [98]. New hypopituitarism also develops in a time-dependent manner reaching 30% at 6 years [99]. Radiological tumor control is obtained in most cases.

A recent metaanalysis [100] of 30 studies including 2464 patients compared the results of FRT and RS. Although a direct comparison is hindered by different levels of hormonal hypersecretion and irradiated volume, RS seems to be associated with a non-significant trend towards better suppression of IGF-I values and remission rates. In addition, hypopituitarism also seems to occur less frequently after RS than after FRT, once again without reaching significance. Long-term toxicity (over 10 years) of irradiation on cerebral tissue is still under evaluation [101]. Neuroradiological changes in the white matter of patients submitted to radiation therapy are a matter of concern in relation to cognition, vascular alterations, and the development of secondary tumors.

Withdrawing GH-suppressive treatment during irradiation, in order to allow the full action of radiation on an active cell, is still an unresolved issue.

Due to the high efficacy of pharmacological treatment for the control of disease, the long latency of the radiation effect, and the drawbacks of long-term toxicities, irradiation should be reserved for patients with aggressive disease or who show resistance/intolerance to available drugs or offered to those willing to have a definitive cure thus cutting costs of life-long medical therapy.

Patients should be monitored at least yearly, to evaluate the efficacy and safety of irradiation. If IGF-I levels during active treatment are below the median of normal range, ongoing treatment for acromegaly should be tapered and eventually withdrawn. The pituitary function should also be monitored as appropriate [102], in order to highlight timely the need to start replacement treatment if not already ongoing.

We recommend irradiation in patients with aggressive disease or resistance (or intolerance) to drugs.

We suggest considering irradiation in patients willing to have a definitive cure regardless of sensitivity to drugs.

We recommend that the technique of irradiation should be selected according to the size of residual adenoma, and proximity to the optic pathways.

We recommend that irradiation, regardless of technique, should be administered by a skilled operator.

We recommend a yearly follow-up to evaluate the efficacy and safety of previous irradiation.

5.5. How to Manage Aggressive Cases

The most common clinical presentation of aggressive pituitary tumors is early recurrence after initial pituitary surgery, rapid local growth and tumor extension despite optimal standard therapies combining surgery, drugs and irradiation [103-105]. Since pituitary carcinomas can only be identified by the presence of distant metastases [106], it has been proposed that aggressive pituitary tumors can be considered as tumors with malignant potential without metastasis [107].

Aggressive pituitary adenomas are challenging to manage. A multimodal approach is required [105, 108] however it is still a matter of debate as to where the line should be drawn to define who should be aggressively treated from the start, because no single biomarker has been found to independently predict aggressive behavior [109].

If the disease is still uncontrolled in terms of hypersecretion and tumor size after first-line surgery and standard maximal medical therapy, debulking pituitary surgery and/or radiation should be considered (see 5.2 and 5.4).

Lastly, temozolomide (TMZ) should be considered [105]. TMZ is approved for the treatment of aggressive pituitary tumors and carcinomas, at the standard dosing regimen of 150-200 mg/m^2 daily for 5 days every 28 days. Methylguanine methyltransferase expression has been associated with resistance to TMZ in the treatment of gliomas, however, its determination is not widely available and thus it should not be taken into account in selecting patients with pituitary tumors for treatment [110, 111]. The lack of tumor volume response after three cycles predicts further resistance to this treatment. There are poorer results of TMZ in somatotroph adenomas than in non-functioning adenomas [112-115].

Radioreceptorial treatment is based on the delivery of a toxic dose of radiation, to specific neoplastic cells expressing SSTR, using radiolabeled analogs, with agents such as ^{90}Y or ^{177}Lu. The limited evidence from case reports to date in time does not yet enable any conclusions to be drawn [116, 117].

We recommend multimodal intensive treatment of patients with aggressive disease.

We recommend referral of patients with aggressive disease to centers with specific expertise in the field.

5.6. General Strategy

The therapeutic management of acromegaly always requires a personalized strategy.

TSS by an expert neurosurgeon is the primary treatment mode for most patients with acromegaly, with either micro or macroadenoma, especially if neurological complications (visual damage, intracranial hypertension, cranial nerve involvement) are involved. A second operation should be proposed only to patients in whom the first operation was fully ineffective leaving a large remnant or in the very rare cases of aggressive tumor not controlled by medical therapies.

In patients with widely-invasive adenoma and expected poor surgical outcome, poor clinical conditions or who refuse surgery, primary medical treatment should be offered. First-generation depot SSAs give the best results and should

be given at the maximum dose to obtain the greatest GH/IGF-I inhibition.

Cabergoline should be reserved for patients with mild GH/IGF-I hypersecretion, irrespectively of PRL levels.

TSS should be recommended in patients who were not deemed to be good surgical candidates in whom primary medical treatment did not lower IGF-I to <120-130% ULNR and/or did not control pituitary tumor size.

Patients with persistent pathologic GH/IGF-I levels after surgery should be treated with pharmacological agents: first-generation depot SSA or cabergoline (if hormonal hypersecretion is mild), either alone or combined in those showing partial response to SSAs. Patients who do not reach hormonal targets with this strategy should be offered two alternative options: a) pasireotide LAR, regardless of their partial sensitivity or full resistance to first-generation SSA; b) PegV, as a monotherapy or combined with SSA if a large adenoma remnant is present. Various factors should be considered in this decision, such as glucose metabolism derangement, tumor size and location, drug cost, and individual preferences.

Pasireotide LAR should be strongly recommended in patients with headaches who are unresponsive to first-generation SSAs.

Focused beam RS is a valuable option for patients with minimal surgical remnant who wish to be free from long-term medical therapies. Patients with persistent disease activity or tumor growth despite surgery or medical therapy should be irradiated with the appropriate technique, according to the size and location of the remnant tumor.

The individualized strategy for the management of acromegaly patients should, in any case, consider all the costs of each option. This should not be limited to the raw cost of any drug (or procedure), but should always include an integrated evaluation of QoL, the management of comorbidities and possible side effects, workdays lost, *etc*.

CONCLUSION AND PERSPECTIVES

Acromegaly is a rare disease, and is likely to be underdiagnosed; moreover, the diagnosis is often delayed. The outlook for patients after diagnosis has dramatically changed in the last few decades due to improved neurosurgical techniques, new drugs, and increased awareness of the systemic complications that need to be specifically addressed.

Several tasks for the future need to be highlighted. The index of suspicion should be increased among general practitioners and other specialists aimed at an early diagnosis before the development of irreversible complications, above all of the skeletal and joint system. New tools, such as the automated analysis of body images [118] or new clinical scores [119, 120], might be of help.

An individually tailored approach to treatment should be pursued, in order to reduce therapeutic inertia and accelerate control of the disease. Patients with aggressive or complicated disease should certainly be referred to centers with highly skilled multidisciplinary experience. Hopefully, peripheral centers should become part of an integrated network. National or European registries might be helpful to examine the natural history and long-term outcome of the disease. Collaboration with patients' associations will add value to the management of the disease and address unmet needs.

A few drugs or novel modalities of treatment are in the pipeline and may be available in the next few years: oral octreotide [121], long-acting SSAs to be injected quarterly [122], and antisense oligonucleotides [123]. Molecular aspects of pituitary adenoma biology, such as SSTR profiling, is an area of intense investigation which may in the future help the clinician to select the appropriate treatment in the individual patient.

With the increasing availability of new therapeutic tools that have already or will soon meet therapeutic targets in most cases, the challenge will be to pay increased attention to the QoL of these patients [124]. This will involve taking into account the patients' requests to address specific problems that they perceive as crucial, which may often have been overlooked by their physicians.

LIST OF ABBREVIATIONS

ATG	=	Autogel
D2R	=	Dopamine Receptor Type 2
FRT	=	Fractionated Radiotherapy
GH	=	Growth Hormone
IGF	=	Insulin-like Growth Factor
LAR	=	Long-Acting Repeatable
LoE	=	Level of Evidence
MRI	=	Magnetic Resonance Imaging
PAOLA	=	Efficacy and Safety of Pasireotide Long Acting Release versus Octreotide LAR or Lanreotide Autogel in Patients with Inadequately Controlled Acromegaly
PegV	=	Pegvisomant
QoL	=	Quality of Life
RCT	=	Randomized Controlled Trial
RS	=	Radiosurgery
SSAs	=	Somatostatin Analogs
SSTR	=	Somatostatin Receptor Subtype
TMZ	=	Temozolomide
TSS	=	Transsphenoidal Surgery
ULNR	=	Upper Limit of Normal Range

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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- Alessandro Bozzao, Giovanni Lasio, Vincenzo Toscano, and Michele Zini report that they do not have any relevant financial relationships with any commercial interests.
- Maria Rosaria Ambrosio reports registration fees for scientific meetings from Ipsen, Novartis, Pfizer, and Savio Pharma
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