Acromegaly: a review of current medical therapy and new drugs on the horizon

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Acromegaly is a disease that results from a growth hormone (GH)–secreting pituitary tumor. Clinically, the disease is characterized by excessive skeletal growth, soft tissue enlargement with disfigurement, and increased risk of cardiovascular death. The goals of treatment are the removal or reduction of the tumor mass via surgery and normalization of GH secretion. Another treatment goal is the preservation of normal pituitary function if possible.

Transsphenoidal surgery by an experienced neurosurgeon is usually the first line of therapy, especially for small tumors. Surgeon expertise is crucial for outcome, with dedicated pituitary surgeons having better results. However, overall cure rates remain low because patients with these tumors usually present at an incurable stage. Therefore, medical therapy to control excess GH secretion plays a significant role in a large proportion of patients with acromegaly who are not cured by surgery or other forms of therapy, such as radiotherapy, and/or are awaiting the effects of radiotherapy. If surgery is not curative, lifelong monitoring and the control of excess GH is usually necessary by a care team experienced in handling this chronic disease.

In the past decade major progress has occurred in the development of highly specific and selective pharmacological agents that have greatly facilitated more aggressive management of active acromegaly. Treatment approach should be individualized and take into consideration a patient’s tumor size and location, symptoms, comorbid conditions, and preferences. Because a surgical cure can be difficult to achieve, all patients, even those with what seems to be a clinically and biochemically inactive disease, should undergo long-term biochemical testing and pituitary MR imaging. (DOI: 10.3171/2010.7.FOCUS10154)

KEY WORDS • acromegaly • pituitary tumor • transsphenoidal surgery • growth hormone

Acromegaly was previously considered a rare disease, with a prevalence of 40–70 cases per million persons and an annual incidence of 3–4 new cases per million persons.59,77 However, recent European studies suggest that clinically significant pituitary adenomas occur in 1 case per 1064 people. With GH-secreting tumors constituting at least 10% of benign pituitary tumors, the calculated incidence could be 77.6 cases per million inhabitants. Furthermore, a provocative German cross-sectional epidemiological study96 in almost 7000 unselected primary care patients documented a prevalence of biochemical acromegaly of 1043 per million persons. Acromegaly screening in that study was performed by measuring IGF-I, and most cases were further confirmed by additional testing. Thus, acromegalic patients are theoretically more prevalent than previously thought,39,44 and in our opinion, this is clearly conceivable. Nonetheless, more studies are needed to establish an accurate incidence.

The nonspecific and protean symptomatology of acromegaly often results in late diagnosis, that is, 4 to > 10 years after initial symptom onset. Besides the local mass effect of the pituitary tumor, acromegaly results in multiple metabolic and “structural” dysfunctions.

Surgery, medical therapy, and radiation have specific advantages and disadvantages that should be weighed and tailored very carefully for each patient. Surgery is considered the mainstay of therapy for most, whereas medication is reserved for patients with persistent excess GH secretion uncontrolled by surgery. In selected cases, primary medical therapy is also an option, and radiotherapy remains a third line of treatment.84,79 Blood tests using serum GH and IGF-I remain the backbone of determining cure or control of the disease. Recently, consensus guidelines regarding the diagnosis and treatment of acromegaly were published.34,55,79

Abbreviations used in this paper: DA = dopamine agonist; DR = dopamine receptor; D2R = dopamine receptor 2; GH = growth hormone; GHRA = GH receptor antagonist; IGF-I = insulin-like growth factor–I; LAR = long-acting release; OGTT = oral glucose tolerance test; SSA = somatostatin analog; SSTR = somatostatin receptor subtype.
In this review we focus on the medical treatment of acromegaly, including novel concepts and experimental therapies, and we emphasize our personal experience.

Goals of Therapy

Acromegaly is a severe disease with increased rates of morbidity and mortality if not treated appropriately. Epidemiological studies estimate the excess mortality rate as approximately 2-fold, attributed primarily to cardiovascular, cerebrovascular, and respiratory disease. A potential confounding mortality factor in patients appears to be the presence of hypopituitarism, mainly adrenocorticotropic hormone deficiency.

Earlier studies suggested that GH levels < 10 ng/ml,115 and later ≤ 5 ng/ml,78 were adequate for control. Based on newer data, these values are now associated with mortality rates above those in the normal population. Growth hormone concentrations < 2.5,12,68,85 < 2,6,60 or < 1 ng/ml are associated with mortality rates comparable with those in the normal population. Five epidemiological studies investigated IGF-I as a predictor of increased mortality, although not everyone agrees that IGF-I is predictive of death.6,12,60,68,103 Swearingen et al.,103 in 1998, were the first to suggest that a normal IGF-I level in patients with acromegaly predicted a normal expected mortality rate.

A comprehensive treatment strategy should alleviate pituitary tumor effects, normalize GH and IGF-I hypersecretion, improve associated comorbidities, and reverse the increase in mortality risk, all while preserving normal pituitary function (Table 1).

Surgery remains the first treatment of choice for patients with acromegaly, given 2 caveats: the need for an experienced surgeon and the tumor’s appearance on MR imaging. In the hands of an inexperienced surgeon, the results of surgery can be quite disappointing. If an experienced surgeon is not available, medical therapy can be offered to the patient as first-line therapy. If the tumor has invaded the cavernous sinus or for other reasons is not completely resectable, medical therapy can be offered as a first-line treatment or in addition to surgery.

Surgical treatment also offers a significant advantage: a final pathological diagnosis. The pathological distinction between different types of GH-secreting tumors can impact the response to therapy as well as prognosis making; therefore, accurate pathological classification is important. Growth hormone–producing tumors range from well-demarcated slowly growing microadenomas to large, more rapidly growing macroadenomas. They vary in morphology and can be separated into several different types: tumors that secrete only 1 GH (monohormonal somatotroph adenomas), tumors that secrete GH and prolactin (bilateral mammosomatotroph adenomas), and silent GH-secreting adenomas (express GH in the tumor without GH hypersecretion or acromegaly). Monohormonal somatotroph adenomas represent the majority of these lesions (90%) and can be further classified as densely granulated or sparsely granulated. Densely granulated tumors are composed of well-differentiated somatotrophs with positive staining for GH when using an immunoperoxidase technique and an electron microscope appearance similar to nontumoral cells. They have a better prognosis overall with slower growth rates, are easier to remove, and recur less frequently after surgery. Sparsely granulated tumors consist of less differentiated cells with positive GH staining but electron microscope characteristics different from normal cells. The sparsely granulated type is prevalent in younger patients and appears to grow more rapidly.

Pituitary GH-secreting cells have 5 SSTRs: SSTR-1 to SSTR-5, with receptors SSTR-2 and SSTR-5 predominant (90%–95%) in GH-secreting tumors.20

<table>
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<th>Parameter</th>
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<th>GHRA</th>
<th>DA</th>
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<td>best agent to improve glucose control</td>
<td>caborergoline use requires echocardiogram heart valve monitoring</td>
<td>slightly increased incidence of stimulating a new tumor in radiated bed</td>
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</table>

* Note that no single technique is superior. Adapted from Melmed S: Medical progress: acromegaly. N Engl J Med 355:2558–2573, 2006. Surgery, medical therapy, and radiation have specific advantages and disadvantages that should be weighed and tailored very carefully for each acromegalic patient. Percentages represent the proportion of patients who have positive results after each treatment.
† Transphenoidal surgery.
‡ At 10 years after treatment.
The density and expression of SSTRs also have potential clinical significance as clinical predictors of response to pharmacotherapy with SSAs. Somatostatin analog resistance is observed in about one-third of tumors and could be related to density reduction or different receptor expression. In 1 study, for example, both SSTR-1 and SSTR-2 had higher expression levels in patients with normalized GH and IGF-I after treatment with SSAs, and SSTR-3 expression correlated with tumor shrinkage as well. Selecting which SSA to use may, in the future, depend on SSTR analysis of the surgical specimen.

All of the above emphasizes the importance of accurate morphological classification using immunohistochemistry and/or electron microscopy, which in our opinion should be performed on all pituitary pathology specimens.

Medical Therapy

Three drug classes are available to treat acromegaly (Fig. 1), each with unique advantages and disadvantages. In patients with uncontrolled hormonal levels after surgery, SSAs are the treatment option of first choice. Dopamine agonists and GHRAs are generally indicated after SSA failure.

Somatostatin Analogs

Somatostatin acts as an endocrine inhibitor to a number of endocrine cells including GH-secreting pituitary cells, pancreatic beta cells releasing insulin, and a number of gastrointestinal tract hormones. Somatostatin ligands or “analogs” bind with varying affinity to the 5 SSTRs described above and mimic the GH suppressive effects of native somatostatin. A potential added benefit of SSAs is their antiproliferative effect.

Somatostatin analogs represent the mainstay of medical treatment for acromegaly, and most pituitary centers now have 25 years of experience with their use. Three SSAs are approved for use in the US: short-acting octreotide, octreotide LAR (Sandostatin LAR), and Somatoline Depot (lanreotide Autogel; Table 2). Octreotide was first approved for use in the US in 1995, followed by octreotide LAR in 1998 and lanreotide in 2007.

Short-Acting Octreotide

Octreotide is approximately 20 times more potent than native somatostatin and has a half-life of 1.5 hours. It is administered as a subcutaneous injection 3 times a day with an immediate biochemical response, suppressing both basal and stimulated GH secretion for up to 5 hours.
With the development of long-acting SSAs, short-acting octreotide is rarely used, except in the acute octreotide test.49 We consider acute suppression tests valuable tools for evaluating a patient’s tolerance of therapy, but their prognostic value in predicting long-term response, despite initial reports,67 is limited.

**Octreotide LAR**

Octreotide LAR is a formulation consisting of octreotide incorporated into microspheres of a slowly dissolving polymer that provides smooth and reliable steady-state kinetics when administered intramuscularly once a month.102 The injection of 20–30 mg results in peak drug levels at 28 days with integrated GH suppression for up to 49 days.38 The pharmacodynamics suggest that although GH suppression will be observed after the first dose, maximal suppression is not observed until after the administration of 3 doses.102 This timeframe should be kept in mind by clinicians when assessing the response to a given dose. Accurate drug administration is imperative, and a dedicated physician-nurse care provider team is essential for long-term care.

The 2 largest studies of octreotide LAR37,72 compiled 261 patients, with more than one-half pretreated with short-acting octreotide and the remainder naïve to medical treatment; GH suppression to < 2.5 μg/L and normal IGF-I was achieved in 63%–75% of patients.

**Lanreotide Autogel**

A recent development has been the introduction of a supersaturated aqueous formulation, lanreotide Autogel, in a prefilled syringe that requires deep subcutaneous administration every 28 days. Lanreotide has a linear pharmacokinetic profile over a dose range of 60–120 mg after both single and repeat injections.79 This new formulation has the potential to increase dosing intervals, and the user-friendly characteristic for the patient to self-administer45,75 (or a partner to administer) could result in improved compliance.

A randomized placebo-controlled study in an unselected population (99 patients) published in 201040 showed that lanreotide Autogel was effective in controlling both GH and IGF-I hypersecretion: 54% of patients had normalized IGF-I and 38% had both normalized IGF-I and a GH level ≤ 2.5 ng/ml. This drug was well tolerated by all patients in the long term.

Similar to other SSAs studied, patients who were not naïve to medical treatment at the beginning of the study were more likely to respond. This study also confirmed an improved response in patients with prior pituitary surgery and less severe acromegaly at baseline.

It is difficult to appreciate the true efficacy of SSAs in achieving biochemical control due to varied study entry criteria and desirable cutoff goals. A 2005 meta-analysis by Freda et al.49 showed that overall GH and IGF-I were normalized in 49%–56% and 48%–66% of patients, respectively, with the efficacy of octreotide LAR higher than that of a slow-release lanreotide (not used in the US). Note, however, that Freda and colleagues’ study was flawed by the inclusion of more than 50% of patients who were preselected with previous octreotide responsiveness.82 The currently available SSAs octreotide and lanreotide seem equally effective,3,105 with the majority of patients achieving symptom control and biochemical control being achieved in approximately one-half of unselected patients. Further meta-analysis of prospective randomized trials on the efficacy of each SSA with respect to GH control and tumor shrinkage is warranted.

Somatostatin analogs are generally safe and well tolerated.78 The most frequent adverse events of SSA use are abdominal symptoms (usually improving over time), glucose intolerance, and gallbladder sludge or stones.

Other potential drawbacks of SSA use are its high cost and patient compliance. In an Italian study, however, the cost of caring for patients who did not respond to SSA was much higher40 than for those who did respond. Recent evidence has suggested that these agents can be used at lower doses or at less frequent intervals with obvious cost and compliance implications. Both octreotide LAR and lanreotide have been successfully used at 6- to 8-week intervals.92,107
Predictors of Biochemical Control

The selection of patients for treatment with SSAs has changed over time. A report by Bevan et al. in 2002 suggested that the control of GH and IGF-I was unlikely in patients with a GH level > 20 ng/ml and an IGF-I level > 900 ng/ml. On the other hand, in 2006 Cozzi et al. showed in 110 patients treated with octreotide LAR that the untreated IGF-I concentration, whether very high or low, did not predict response. Furthermore, in a 2010 report by Melmed et al., patients with less severe acromegaly at baseline had better responses to treatment with lanreotide. No reliable predictive factors relating to a final dose frequency were identified in any studies and thus stressing the importance of individual tailoring of the dosing regimen for each patient.

Tumor Shrinkage

A number of studies have reported tumor shrinkage in patients with acromegaly treated with SSA therapy, both adjunctively and primarily. This shrinkage can be significant (20%–80% in about one-third of patients) but unpredictable (Fig. 2).

Tumor reenlargement after SSA discontinuation has also been noted in some cases. Several mechanisms have been proposed for the observed reversible tumor shrinkage; however, the exact cellular mechanism remains unclear.13,32,79

Primary therapy, as expected, has more impressive shrinkage results.6 In a prospective study in 99 patients with acromegaly, 75.5% experienced ≥ 25% tumor shrinkage after 12 months, while a significant increase in tumor mass occurred in only 2.1% of the patients. The best predictor of tumor shrinkage was posttreatment IGF-I levels, with patients having the lowest IGF-I level also demonstrating the best tumor shrinkage. A longer prospective study confirmed this observation; the higher the basal GH values and the greater the GH/IGF-I changes, the greater the tumor shrinkage. The authors reported tumor shrinkage of 62% ± 31% (range 9%–100%) in 82.1% of patients.

Use of SSAs in Primary Therapy

Somatostatin analogs may be equally effective if used as adjuvant or initial therapy. Most studies examining the efficacy of long-acting SSAs have focused on patients after surgery and radiation treatment. More recently, however, a large cohort of patients has been treated with primary/de novo therapy. For microadenoma cases in which the surgical cure rate can reach 80%–90%, primary SSA therapy should be used only in those patients who refuse to undergo or have contraindications for surgery. At this time, there are no randomized controlled studies that compare primary medical therapy with initial surgery.

A large German study, ACROSTUDY 2008, showed that pituitary surgery in 554 patients normalized GH and IGF-I levels in 54.3% and 67.2% of patients, respectively. This approach was clearly more effective than the 36.3% (normalized GH) and 30.5% (normalized IGF-I) obtained by using primary SSA in 145 patients. In some of the SSA-treated patients, the control rate increased slightly with a longer administration of medical therapy (> 360 days). In a recently published 5-year primary SSA trial by Colao et al., differing results were achieved. In all 45 patients on prolonged octreotide LAR therapy (28 patients) and lanreotide therapy (17 patients), successful control of GH and IGF-I was achieved, and hypertension, cardiac function, and lipid abnormalities improved. Interestingly, glucose metabolism was not affected despite biochemical control. Unfortunately, these data represent only those patients who were fully responsive to SSA, as another 31 patients unresponsive to SSA therapy underwent surgery within 1–2 years.

Overall, we conclude that SSAs are a good primary treatment option in carefully selected patients.

Pretreatment With SSAs

It has been suggested that SSA treatment prior to surgery can reduce surgical risks and potentially improve surgical cure results. While symptomatic improvement and reduction in soft tissue swelling have been well documented, the effect of SSA pretreatment on surgical outcome remains unclear at present. In the ACROSTUDY 2008, for example, SSA treatment before surgery was shown to improve surgical outcome only marginally.

One of a few well-designed prospective studies by Carlsen et al. suggested that with pituitary macroadenomas, SSA pretreatment improves surgical outcomes; however, the surgical cure rate (23% achieved IGF-I normalization, and just 16% by using a combined criteria, that is, adding a GH nadir during OGTT ≤ 1.0 ng/L) was much lower than the average reported in the literature (between 50% and 70%). Most probably, the rela-

Fig. 2. Coronal post-Gd T1-weighted MR images obtained in a 31-year-old woman with a GH-secreting pituitary adenoma. She underwent partial tumor resection due to cavernous sinus involvement. A: Preoperative. B: Three months postoperative. C: Six months after starting SSA. D: One year post-SSA treatment.
tively low cure rate combined with just the few microad-
emonas included in the study played a role in the negative
effects of pretreatment in pituitary microadenomas. Inter-
estingly, in contrast with other studies,\textsuperscript{101} Carlsen et al.\textsuperscript{32} noted that SSA pretreatment increased the consistency of the tumor, making the tumor more fibrotic and easier to identify during surgery.

**Role of Surgical Debulking**

Convincing evidence has emerged showing that the efficacy of medical therapy may be improved if the majority of the tumor is removed (that is, debulked) despite incomplete surgical removal. Tumor debulking is often used with SSA therapy when GH is partially but not completely controlled with treatment. In these cases, tumor debulking may allow SSA therapy to reduce GH and IGF-I levels into the normal age-adjusted range.\textsuperscript{27,66,114} The removal of more than 75\% of the tumor load in a retrospective study in 86 patients increased the response to SSAs by more than 25\% of the tumor load in a retrospective study in 86 patients increased the response to SSAs.

It has also been suggested that patients with a high GH concentration and a large tumor could benefit more from debulking surgery.\textsuperscript{87} In our opinion, surgical debulking has an important role to play in the treatment algorithm, and we routinely use this approach in our practice.

**Dopamine Agonists**

For many years, the only drugs available to treat acromegaly were DAs such as, for example, bromocriptine. This class of drug causes the stimulation of GH release in healthy individuals but leads to paradoxical suppression of GH hypersecretion in a proportion of patients with acromegaly. The effectiveness of DAs in the control of GH secretion appears to correlate with the expression of D2Rs within the tumor rather than with the presence of prolactin.\textsuperscript{30}

Experience with bromocriptine is well documented;\textsuperscript{42,112,113} however, only approximately 10% of patients achieve safe GH and normal age-adjusted IGF-I levels despite using substantially higher doses than those required for the successful treatment of prolactin-secreting tumors. Side effects often limit the ability to even use this higher dose.

Cabergoline is a more potent DA and better tolerated than bromocriptine. A wide range of satisfactory biochemical control with cabergoline alone has been reported.\textsuperscript{29,50,64} The highest rate of response, up to 39% of patients,\textsuperscript{1} has not been reproduced elsewhere, although clinical improvement\textsuperscript{67,68,31} and substantial reductions in GH and IGF-I levels have been observed in the majority of patients studied.

The potential for the long-term use of cabergoline (especially at the higher doses usually required in patients with acromegaly) to cause cardiac valvular damage cannot be ignored.\textsuperscript{50} However, cabergoline administration at a dose < 3 mg/week appears safe.\textsuperscript{24} Future studies will help to clarify DA-induced cardiac valvular disease. A conservative approach for now would be to use bromocriptine rather than cabergoline or to use low-dose cabergoline in combination with other drugs. If cabergoline is used, a pretreatment echocardiogram should be obtained to determine the anatomical integrity of heart valves; and if one or more valves are deemed incompetent, cabergoline should not be used. Heart valve incompetency has been reported as an adverse effect associated with acromegaly independent of DAs.\textsuperscript{86,109}

In summary, the general advantages of DA use are oral administration, relatively low cost, and no associated hypoglycemia; however, overall efficacy is quite limited. We consider DA use effective in a subset of patients with very modest IGF-I elevations. We also recommend DA as a possible first-line therapy in patients with prolactin–secreting tumors or as a combination therapy.

**Growth Hormone Receptor Antagonist**

The GHRA pegvisomant directly inhibits peripheral GH action by interfering with the functional dimerization of the 2 GH receptor subunits, thus blocking the signal for IGF-I production.\textsuperscript{69} In initial clinical trials, lowered or normalized IGF-I was observed in about 90% of patients.\textsuperscript{105,110} However, recent data from a large 5-year observational study of pegvisomant use\textsuperscript{104} has revealed a much lower IGF-I normalization rate (70% of patients), most probably due to inadequate dosage (more than two-thirds of the patients were taking the lowest dose). The cause of dose titration failure seems unclear; however, it does raise a very interesting point about the importance of both initiating the right treatment and further close monitoring.

In a 1-year, open-label randomized study of 118 patients, pegvisomant and octreotide LAR were equally effective in normalizing IGF-I in the overall population, but pegvisomant was more effective in patients with a higher baseline IGF-I. Treatment-related adverse events were mild to moderate in both groups.\textsuperscript{53} In that study, as in previous trials,\textsuperscript{105,111} pegvisomant had a more favorable effect on the parameters of glycemic control and thus has even been suggested as first-line medical therapy in patients with glucose metabolism abnormalities.\textsuperscript{7}

The adverse events most frequently attributed to pegvisomant are disturbed liver function tests and injection site reactions.\textsuperscript{106} Lipodistrophy\textsuperscript{18,93} and acute hepatotoxicity\textsuperscript{108} have also been reported.

Pegvisomant is unique in that the drug does not lower GH levels—in fact, levels are raised due to feedback mechanisms—thus making IGF-I the only available marker for disease activity. Pegvisomant has no known antiproliferative effects and, despite some concern,\textsuperscript{12} has not been associated with tumor growth overall.\textsuperscript{57,65} In a very recent 2-year German prospective study\textsuperscript{12} that included serial MR images, a tumor volume increase of > 25% during the study was observed in 3 (4.9\%) of 61 patients. (Note that approximately two-thirds of the initial group completed that study.) All tumor changes were observed during the first year of enrollment. Interestingly, all 3 patients had prior SSA treatment, revealing a potential rebound effect of stopping this treatment and/or the natural history of aggressively growing pituitary tumors. Longer studies on
Acromegaly: current medical therapy and new drugs

naïve patients to those on medical therapy would be necessary to definitely answer this question. We recommend continued long-term surveillance of tumor volume in all patients treated with pegvisomant, particularly in non-radiated patients.

The selection of patients for GHRA therapy has been further defined. In most cases, pegvisomant should be reserved for SSA nonresponders, patients intolerant of SSAs, and patients whose diabetes is worsened by SSAs or who are considered to be taking combination therapy.

Combination Therapy

Over the years newer therapeutic options have included combination therapies with DAs, SSAs, and the GHRA pegvisomant.

Somatostatin Analogs and DAs

To overcome resistance to 1 agent, the combined use of SSAs and DAs has been extensively studied with various results. The addition of high doses of cabergoline to SSA treatment has been shown to improve the response to GH in patients whose GH levels were not previously controlled with a maximum dose of SSA. The beneficial effects of cabergoline in combination with SSAs occur even when pretreatment prolactin levels are normal and/or there is no tumor GH/prolactin coexpression.53 Randomized prospective controlled studies are needed to confirm the effects of this combined regimen.

Somatostatin Analogs and GHRA

The addition of weekly pegvisomant to SSA treatment has been shown to control disease in the majority of patients with no significant increase in adverse effects. A combination of long-acting SSAs once monthly and pegvisomant once weekly (up to 80 mg, median 60 mg) in 26 patients with active acromegaly normalized IGF-I in 18 (95%) of 19 patients who completed 42 weeks of treatment. This combination therapy has also been successfully used in patients resistant to SSAs.83 Long-term safety data are now available for 86 patients (follow-up 29.2 ± 20.2 months; median dose of 60 mg pegvisomant administered weekly), added to data for patients previously treated with SSA for at least 6 months.83 Transient elevation in liver enzymes was observed in 23 (27%) of 86 patients regardless of the cumulative dose of pegvisomant, but enzymes subsequently became normal after discontinuing the drug. This study also showed tumor shrinkage of > 20% in 19% of patients. The highest percentage of tumor shrinkage was observed in those who received primary medical treatment.83 The possibility of lower doses of both SSAs and GHRA must be investigated further. The overall effects on the cost of this combination have been debated.

Elevation in liver enzymes is observed more frequently with combination therapy, and long-term safety should be established before definite treatment recommendations are made.

In our opinion, the decision to use monotherapy or combination treatment should depend on individual patient circumstances. Tumor shrinkage with SSAs would be a good reason to continue SSAs, whereas worsening glucose control could tip the balance toward GHRA use.

New Therapies on the Horizon: Drugs in Clinical Trials

The role of SSTRs and DRs as molecular targets for the treatment of pituitary adenomas is well established. More recently, however, work on the expression of SSTR and DR subtypes, their coexpression, and their functional interface via dimerization has opened new perspectives for patients currently unresponsive to or intolerant of clinically available drugs. Research into an additional long-term delivery method (compared with the monthly injection of long-acting octreotide) as well as potential patient compliance and cost improvement is underway.

Multiligand SSA Pasireotide

A relatively high proportion of patients are resistant to octreotide and lanreotide, which could be explained in part by variable tumor expression and/or decreased density of SSTR-2. The multiligand SSA pasireotide (SOM 230) is a novel somatostatin analog (mimetic) with a unique structure. It has a very long plasma half-life, potent in vitro and in vivo inhibitory effects on GH and IGF-1 release, a high binding affinity to SSTR-1, -2, -3, and -5, and up to a 20-fold greater affinity for SSTR-5 than octreotide. Therefore, it is a promising therapeutic candidate with several potential advantages over currently used SSAs. The high affinity of pasireotide for both SSTR-5 and SSTR-1 could be important in GH-secreting adenomas resistant to current therapy. Furthermore, binding and functional synergy between SSTR-2 and SSTR-5 could be beneficial even in responsive tumors.

Phase I and II trials on GH-secreting tumors have been encouraging with good biochemical control and “significant” tumor shrinkage, making SOM230 a promising candidate. There are, however, potential concerns related to glucose intolerance. The safety and efficacy of pasireotide LAR versus octreotide LAR in patients with active acromegaly is presently being studied in a large, Phase III, randomized, blind multinational study (www.clinicaltrials.gov).

A future role for pasireotide remains to be determined, but its use in the treatment of octreotide-resistant tumors, especially large ones, seems most likely.

Somatostatin-Dopamine Chimeric Ligand

A functional interaction between D2R and SSTR-5 has been reported recently, with the subsequent development of a new chimeric compound containing structural elements of both somatostatin and dopamine, that is, dopastatin. The exact mechanism by which combined somatostatin-dopamine treatment has a synergistic effect on GH suppression is not completely clear, but Saveanu et al. suggested crosstalk of the G-coupled receptors or dimerization on the cell membrane/postmembrane level. Nonclinical pharmacological studies have shown that dopastatin is more potent and more effective than oct-
reotide alone or octreotide in combination with cabergoline in suppressing GH secretion, and thus seems a promising approach for acromegaly treatment. Patients who express both SSRT-2 and D2R should be especially suitable for this treatment. As a note of caution, however, discrepancies between the presence of a receptor profile SSTR/D2R and the limited efficacy of an agonist drug has been reported.

After encouraging in vitro results, a study to assess the efficacy and safety of the repeated administration of dopastatin (BIM-23A760) in patients with acromegaly is presently underway in a Phase II multinational clinical trial (www.clinicaltrials.gov).

Extended Delivery of Octreotide Including Octreotide Implants

Another exciting area of research involves changing the delivery system. A Hydron implant delivering octreotide for up to 6 months has been analyzed recently. Two Phase I/II clinical studies have evaluated the pharmacokinetics, efficacy, safety, and drug release characteristics of this octreotide implant in 45 patients with a full or partial response to octreotide. The implant maintained GH at < 5 ng/ml in 94% of patients and achieved normal IGF-I in 60% of patients as compared with octreotide LAR (83% and 51% of patients, respectively). There were no serious or severe adverse events, and all patients completed the study. These results suggest a possible improvement over currently used daily and monthly formulations of octreotide. The implant delivery system is being studied in Phase III multinational clinical trials (www.clinicaltrials.gov).

Overall, it remains to be determined where all of these new therapies will ultimately fit into the treatment paradigm.

Monitoring Therapy

Cutoff Numbers

It is important to note that despite major advances in test methodology and accuracy, the normal value, or target, for the treatment of the GH axis is still controversial. The present trend of lowering the cutoff seems to correlate with disease outcome, and clinicians should be aware of the limitations of each test.

The general consensus is to lower the IGF-I concentration to within the reference range for the patient’s age and sex and to lower the random serum GH concentration to < 1 or 0.4 ng/ml after a glucose load (OGTT).

Insulin-like growth factor 1 provides a measure of integrated GH secretion, and IGF-I concentrations are closely correlated to GH, although discrepancies remain. It is still unclear which is more important to follow over time: GH or IGF-I.

Therefore, we recommend IGF-I as an excellent end point to assess therapeutic efficacy for both the patient and the physician. Of course, it is critical to use an established IGF-I assay with age- and sex-dependent normal ranges while using the same laboratory every time.

Postoperatively, it may take several months for IGF-I levels to fall into the normal range despite a cure. However, the OGTT can be performed earlier in the postoperative period and can be relied on as early as 1 week after surgery to confirm GH secretion status. Postoperatively, we routinely obtain both IGF-I levels and OGTT results. In cases of discordant results, we rely on GH values (random or GH profile).

Oral glucose tolerance test utility in diabetic patients or in those treated with SSAs has been questioned more recently. As mentioned earlier, there is no use in obtaining GH measurements for patients on pegvisomant.

Frequency of Monitoring

Monitoring frequency should be clearly individualized depending on the initial tumor size, activity of the disease, and type of treatment. Regardless of the therapy used, patients with clinically and biochemically inactive disease should undergo long-term follow-up, biochemical testing, and pituitary MR imaging. Preoperative long-acting SSA treatment may influence the timing of postoperative evaluation.

At a minimum, random serum GH and IGF-I levels should be measured on an annual basis for all acromegalic patients after surgery, since recurrences have been reported 10–20 years after an apparent cure.

Monitoring a patient’s tumor size with serial MR imaging during drug therapy with an SSA, a DA, or a GHRA is also mandatory.

Persistent subtle elevations in GH levels in the presence of normalized IGF-I levels may predict recurrence, despite the remission of coexisting illnesses and normalized IGF-I levels.

Monitoring endogenous pituitary reserve, cardiovascular function (including echocardiographic evaluation), pulmonary status, blood sugar control, and rheumatologic complications is also essential to patient care.

For pegvisomant therapy, liver function tests should be performed monthly for the first 6 months and every 6 months thereafter, since elevated hepatic aminotransferase levels have been reported. Magnetic resonance imaging should be performed every 6 months for the first year and annually thereafter to detect possible continued tumor growth.

Conclusions

Acromegaly is a severe, often chronic disease with increased morbidity and mortality rates if not treated appropriately. It remains a challenging condition to manage, particularly if the disease persists after an initial transsphenoidal surgery. The treatment of patients with persistently active acromegaly has been facilitated over the past decade by the advent of highly specific and selective pharmacological agents, which are sometimes used in combination. It is anticipated that newer somatostatin receptor ligands or chimeric molecules could help control GH hypersecretion in patients refractory to current therapies, and clinical trials are underway. A better delivery system may improve patient compliance. The neurosurgeon should be prepared to discuss the possible need for adjuvant treatment, including medical therapy and/or radiation therapy. Acromegalic patients are best cared for
Acromegaly: current medical therapy and new drugs

at a specialized center by a multidisciplinary neuroendocrine team comprised of neurosurgeons, endocrinologists, radiation oncologists, neuroophthalmologists, and otorhinolaryngologists. No single treatment algorithm applies to all patients. Treatment should be individualized with long-term follow-up. Monitoring both biochemical control (IGF-I and GH levels close to normal) and tumor size is essential. The clinician must think in terms of therapy for today with an expectant eye toward tomorrow.

Disclosure

Dr. Fleseriu has received consultant fees from Novartis Pharmaceuticals, Tercica, Inc., and Endo Pharmaceuticals, and is a principal investigator in clinical trials sponsored by Novartis Pharmaceuticals and Ipsen Pharma. Dr. Cook has received consultant fees from Novartis Pharmaceuticals, Tercica, Inc., and Endo Pharmaceuticals, and is a principal investigator in clinical trials sponsored by Ipsen Pharma, Endo Pharmaceuticals, and Pfizer, Inc.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Fleseriu. Analysis and interpretation of data: Fleseriu, Cook. Drafting of the article: Fleseriu. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors

Acknowledgments

The authors thank Shirley McCartney, Ph.D., for editorial assistance and Andy Rekito, M.S., for illustrative assistance.

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Neurosur Focus / Volume 29 / October 2010

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