Diagnosis and Treatment of Acromegaly: An Update

Nazanin Ershadinia, MD, and Nicholas A. Tritos, MD, DSc

Abstract

Acromegaly is typically caused by a growth hormone—secreting pituitary adenoma, driving excess secretion of insulin-like growth factor 1. Acromegaly may result in a variety of cardiovascular, respiratory, endocrine, metabolic, musculoskeletal, and neoplastic comorbidities. Early diagnosis and adequate treatment are essential to mitigate excess mortality associated with acromegaly.

PubMed searches were conducted using the keywords growth hormone, acromegaly, pituitary adenoma, diagnosis, treatment, pituitary surgery, medical therapy, and radiation therapy (between 1981 and 2021).

The diagnosis of acromegaly is confirmed on biochemical grounds, including elevated serum insulin-like growth factor 1 and lack of growth hormone suppression after glucose administration. Pituitary magnetic resonance imaging is advised in patients with acromegaly to identify an underlying pituitary adenoma.

Transsphenoidal pituitary surgery is generally first-line therapy for patients with acromegaly. However, patients with larger and invasive tumors (macroadenomas) are often not in remission postoperatively. Medical therapies, including somatostatin receptor ligands, cabergoline, and pegvisomant, can be recommended to patients with persistent disease after surgery. Select patients may also be candidates for preoperative medical therapy. In addition, primary medical therapy has a role for patients without mass effect on the optic chiasm who are unlikely to be cured by surgery. Clinical, endocrine, imaging, histologic, and molecular markers may help predict the response to medical therapy; however, confirmation in prospective studies is needed. Radiation therapy is usually a third-line option and is increasingly administered by a variety of stereotactic techniques. An improved understanding of the pathogenesis of acromegaly may ultimately lead to the design of novel, efficacious therapies for this serious condition.

Acromegaly is generally caused by excessive growth hormone (GH) secretion from a pituitary adenoma and is associated with substantial morbidity and mortality. This article includes an overview of GH physiology and pathogenesis of acromegaly, followed by a discussion of current and evolving approaches to the diagnosis and management of acromegaly.

Factors that may predict the response to surgery or medical therapy are reviewed and future directions are discussed.

To compile this review, the authors have conducted electronic literature (PubMed) searches using the keywords growth hormone, acromegaly, pituitary adenoma, diagnosis, treatment, pituitary surgery, medical therapy, and radiation therapy (between 1981 and 2021). Articles were cited at the authors’ discretion.

GROWTH HORMONE PHYSIOLOGY

Pulsatile GH secretion by anterior pituitary somatotroph cells is normally under dual control exerted by hypothalamic peptides, including stimulation by growth hormone—releasing hormone (GHRH) and inhibition by somatostatin. Ghrelin, predominantly secreted by the gastric fundus but also expressed in the hypothalamus, provides an additional albeit poorly understood stimulus to GH secretion. In healthy individuals, GH is secreted episodically, predominantly during slow-wave sleep or during exercise.
Growth hormone exerts a multitude of effects on metabolism and promotes tissue growth, either directly or indirectly; the indirect GH actions are mediated by GH-induced stimulation of insulin-like growth factor 1 (IGF-1) secretion from hepatocytes and muscle and bone cells, among others, acting in an endocrine or paracrine manner.\(^6\) In healthy individuals, GH secretion is under negative feedback control by circulating IGF-1, most of which is of hepatic origin.\(^4,7,8\)

Growth hormone exerts its actions by binding to its cognate receptor (GHR), a member of the cytokine receptor superfamily.\(^9\) The GHR exists in a dimeric form before ligand binding. On GH binding, the GHR undergoes conformational changes that allow Janus kinase 2 (JAK2) activation to occur, leading to phosphorylation and activation of several signal transducers and activators of transcription (STATs), including STAT 1, 3, and 5, which mediate intracellular GH signaling.\(^9\) Additional GH signaling pathways have been well recognized.\(^10\)

Insulin-like growth factor 1, secreted in response to GH action, mediates its effects by binding to the IGF-1 receptor located in the cell membrane of target cells.\(^11\) On ligand binding, the IGF-1 receptor's intrinsic tyrosine kinase becomes activated, leading to phosphorylation of several substrates (including insulin receptor substrates) and downstream activation of the phosphatidylinositol 3-kinase and Ras-mitogen-activated protein kinase pathways.\(^11\)

### PATHOGENESIS OF ACROMEGALY

In most cases, acromegaly occurs as a consequence of chronic exposure to excess GH, secreted from a somatotroph pituitary adenoma in an unregulated manner.\(^1\) These are typically benign tumors and can be histologically classified as densely granulated, sparsely granulated, acidophil stem cell, and mixed somatolactotroph and mammosomatotroph adenomas.\(^12,13\)

Somatotroph adenomas are generally sporadic.\(^14\) However, familial or syndromic acromegaly occurs in a small minority of patients (Table 1).\(^15\) These include familial isolated pituitary adenoma, multiple endocrine neoplasia 1 and 4, X-linked acrogigantism, hereditary paraganglioma-pheochromocytoma syndrome, Carney complex, and neurofibromatosis 1.\(^15\) Exogenous GH, administered in excess, will recapitulate the phenotype of patients with acromegaly.\(^16\) Very uncommonly, GHRH secretion from an ectopic neuroendocrine tumor or sellar gangliocytoma may drive GH excess from pituitary somatotrophs.\(^17\) Very rarely, ectopic GH secretion from an islet cell tumor or a lymphoma has been reported.\(^18,19\)

Somatotroph pituitary adenomas generally secrete GH autonomously, leading to GH and IGF-1 excess. However, silent somatotroph adenomas are also well recognized and are not associated with a syndrome of hormone excess.\(^20\) Patients whose disease onset precedes epiphyseal fusion develop...
increased linear growth, leading to gigantism. In contrast, patients whose tumors occur after epiphyseal maturation develop acromegaly, characterized by typical facial features (frontal bossing, prominent cheeks and nose, thickened lips, prognathism, widely spaced teeth, and macroglossia), acral enlargement, and organomegaly. In addition, a multitude of manifestations have been associated with chronic GH excess, including cardiovascular (hypertension, ventricular hypertrophy, heart failure, arrhythmias), pulmonary (obstructive sleep apnea), neoplastic (colon polyps, colon cancer, differentiated thyroid cancer), endocrine and metabolic (insulin resistance and diabetes mellitus, oligomenorrhea), and musculoskeletal (vertebral deformities, osteoarthropathy, carpal tunnel syndrome) comorbidities. About 70% of somatotroph adenomas are macroadenomas, defined as tumors exceeding 1 cm in largest diameter. Pituitary macroadenomas may exert local mass effect on the normal pituitary gland or surrounding structures, leading to hypopituitarism, headache, or visual compromise.

**DIAGNOSIS OF ACROMEGALY**

Young patients with excessive linear growth during childhood or adolescence should be evaluated for the presence of GH excess. In adults, the diagnosis of acromegaly should be considered in patients presenting with acral enlargement or
suggestive facial features as well as in those presenting with a constellation of symptoms, signs, or conditions associated with acromegaly, including frequent headache, excessive perspiration, hypertension, sleep apnea, oligomenorrhea, arthralgias, carpal tunnel syndrome, and type 2 diabetes mellitus. A high index of suspicion is needed to consider the diagnosis, particularly in patients presenting earlier in the course of the disease. An interval of several years between symptom onset and diagnosis is common. A longer interval between disease onset and diagnosis has been associated with higher all-cause mortality and a higher number of comorbidities, affirming the importance of early detection and prompt management.

Analysis of facial features on patients’ photographs has been reported to be helpful in detecting acromegaly in patients with subtle features. Machine learning approaches are being studied and may allow earlier identification of patients with this disease. In one study, machine learning methodology could detect acromegaly, based on analysis of facial photographs, with a sensitivity of 96%, a specificity of 96%, a positive predictive value of 96%, and a negative predictive value of 95%.

Serum IGF-1, measured by immunoassay or liquid chromatography/tandem mass spectrometry, exhibits no significant diurnal variation and is the diagnostic test of choice when GH excess is suspected. The test is generally accurate when it is performed in a reliable assay; however, repeating this test is recommended, particularly when the result is borderline or does not fit with the clinical picture. Considering that serum IGF-1 levels decline with advancing age during adulthood, it is critical that reference intervals be carefully established for patients of different age groups. Serum IGF-1 levels normally rise during adolescence as well as in pregnancy, thereby potentially confounding test interpretation in these groups. On the other hand, serum IGF-1 levels can be blunted in patients with acromegaly exhibiting resistance to GH action, including those with advanced liver or kidney disease, severe hypothyroidism, malnutrition, anorexia, and poorly controlled diabetes mellitus, or in women receiving oral estrogen. Estrogen induces suppressor of cytokine signaling 2 (SOCS2) in hepatocytes, thereby blunting GH-mediated signaling and IGF-1 secretion.

Randomly sampled serum GH levels, measured by immunoassays, are generally not recommended for the diagnosis of acromegaly but have been associated with biochemical outcomes of both surgical and medical treatments. Serum GH levels, measured every 30 minutes for 2 hours after the administration of an oral glucose load (75 g), can be helpful in establishing the diagnosis of acromegaly. In most healthy individuals, GH levels decrease to a nadir below 0.4 µg/L after glucose administration (using sensitive immunoassays). In contrast, patients with acromegaly fail to suppress serum GH levels after oral administration of glucose. However, the optimal diagnostic cut point of this test has been a matter of debate. A somewhat higher diagnostic cut point (1 µg/L) for nadir GH levels has been suggested for routine clinical use in the diagnosis of acromegaly, taking into consideration the more limited accuracy of some GH immunoassays currently in use.

Once the diagnosis of acromegaly has been confirmed on the basis of the results of endocrine testing, a pituitary magnetic resonance imaging (MRI) examination should be obtained to detect a pituitary adenoma, which is the cause of acromegaly in most cases. A computed tomography examination of the brain (with special attention to the sella) can be obtained in patients with contraindications to MRI. In one study, 3.2% of patients (6 of 190) with acromegaly had no evident pituitary tumor on standard MRI. Among the rare patients with acromegaly who have no evident tumor on pituitary MRI, serum GHRH levels and cross-sectional imaging of the chest and abdomen can be helpful in detecting an ectopic source.
MANAGEMENT OF ACROMEgiaLY

Overview
Patients with uncontrolled acromegaly experience diminished survival, which has been attributed to increased risks of cardiovascular, cerebrovascular, respiratory, and neoplastic disease.35,36 Patients whose disease is controlled, including those with normal serum IGF-1 and low serum GH levels (random GH level <2.5 μg/L in older polyclonal immunoassays or GH level <1.0 μg/L in newer monoclonal immunoassays), have mortality rates that are indistinguishable from those in the general population.37 Broadly, the goals of treatment in patients with acromegaly include normalization of GH secretion or (at least) GH action as indicated by a normal IGF-1 level as well as by resolution of tumor-induced mass effects, acromegaly-related symptoms, and associated comorbidities, all aiming at mitigating excess mortality while preserving normal pituitary function.38

Management options for patients with acromegaly include pituitary surgery, medical therapy, and radiation therapy (Table 2).38 Pituitary surgery is the cornerstone of treatment for most patients.3 Medical therapy and radiation therapy generally represent second-line and third-line options, respectively, and are typically advised for patients who are not in remission postoperatively (Figure). In addition, preoperative medical therapy may have a role in the management of patients with sleep apnea or

<table>
<thead>
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<th>TABLE 2. Management Options for Acromegalya</th>
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<td>Treatment modality</td>
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<tr>
<td>Transsphenoidal surgery</td>
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<td>Medical therapy</td>
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<td>Somatostatin receptor ligands</td>
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<td>Cabergoline</td>
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<td>Pegvisomant</td>
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<td>Radiation therapy</td>
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aCSF, cerebrospinal fluid; D2, dopamine receptor 2; GH, growth hormone; GHR, growth hormone receptor; IGF-1, insulin-like growth factor 1; SSTR, somatostatin receptor.
bFirst-generation somatostatin receptor ligands (octreotide acetate, octreotide LAR, lanreotide depot, oral octreotide) activate SSTR2 and, to a lesser extent, SSTR5; second-generation somatostatin receptor ligands (pasireotide LAR) activate SSTR1, 2, 3, and 5 (activation of SSTR2 and SSTR5 is considered to be central to drug effectiveness).
Some studies have reported that preoperative medical therapy with somatostatin receptor ligands (SRLs) may improve surgical remission rates. However, methodologic concerns and low remission rates among the groups of patients who underwent surgery without preoperative medical therapy have raised concerns about the generalizability of some of these studies. Select patients may also be candidates for primary medical therapy with SRLs, including those whose tumors do not compress the optic apparatus and are unlikely to be cured by surgery (because of tumor extension into the cavernous sinuses or clivus) and those who decline surgery. Deep learning and other artificial intelligence technologies may be helpful in accurately predicting the response to therapy. In addition to treatment directed at the underlying tumor and control of GH excess, careful attention is needed to identify and to manage acromegaly-associated comorbidities, which may lead to impaired quality of life (even in patients in remission) and excess mortality. To detect such comorbidities, several assessments have been recommended, including blood pressure measurements, electrocardiography, echocardiography, testing for sleep apnea (sleep study), evaluation of glycemia and anterior pituitary function, bone mineral density and vertebral morphometry (by X rays), screening colonoscopy, and assessments of quality of life.

**Pituitary Surgery**

Pituitary surgery is generally carried out transsphenoidally using an endoscope in most cases, although some surgeons may still use an operating microscope. Use of the endoscope may be associated with a higher rate of gross total resection but not a difference in endocrine remission. Pituitary surgery requires substantial expertise to achieve optimal outcomes with regard to endocrine remission and tumor resection while minimizing perioperative complications, including epistaxis, cerebrospinal fluid leak, tumor bed hemorrhage, meningitis, stroke, diabetes insipidus, hyponatremia, and anterior hypopituitarism. Perioperative mortality rates are below 1% in expert hands.

When transsphenoidal surgery is performed by experienced surgeons, endocrine remission can be achieved in up to 90% of patients with acromegaly who have tumors smaller than 1 cm in maximal diameter (microadenomas). In contrast, patients with larger tumors (macroadenomas) achieve endocrine remission in 50% to 60% of cases after transsphenoidal surgery. In addition to surgical expertise and tumor size, tumor invasiveness and serum GH levels predict the likelihood of postoperative remission.

**Medical Therapy**

Current options for medical treatment of patients with acromegaly include SRLs, cabergoline, and pegvisomant (Table 2). Several SRLs and pegvisomant are Food and Drug Administration approved for treatment of patients with acromegaly. Cabergoline has been used off-label in this population of patients.
First-generation SRLs (octreotide acetate, octreotide long-acting release [LAR], lanreotide depot, oral octreotide) and a second-generation SRL (pasireotide LAR) activate distinct subsets of somatostatin receptors (SSTRs), thereby inhibiting GH secretion while promoting apoptosis and exerting antiproliferative effects. These agents signal through both canonical and noncanonical pathways. They engage Gi proteins to inhibit adenylate cyclase and calcium channels while activating potassium channels, leading to membrane hyperpolarization. These events culminate in decreased GH secretion. In addition, SRLs activate pertussis toxin—indepedent G proteins, leading to phospholipase C activation and inositol 1,4,5-triphosphate generation. Furthermore, the tyrosine phosphatases SHP-1 and SHP-2 are activated in response to SSTR activation, as is the tyrosine kinase Src. These pathways culminate in the up-regulation of antiproliferative and proapoptotic pathways that result in antitumor effects.

First-generation SRLs engage SSTR-2 primarily and SSTR-5 secondarily to exert their salutary effects in acromegaly. In a meta-analysis of 90 studies, administration of first-generation SRLs resulted in IGF-1 normalization and GH control in 54% and 55% of 3787 patients with acromegaly, respectively. There was no difference in efficacy between octreotide LAR and lanreotide depot. Studies of first-generation SRLs in unselected patients have reported somewhat lower efficacy with regard to biochemical control (achieved in about 30% to 40% of patients). Approximately 60% of patients with acromegaly controlled on parenteral first-generation SRL therapy maintain biochemical control after being switched to oral octreotide. Some degree of tumor shrinkage has been reported in 53% of 1685 patients in another meta-analysis of 41 studies involving first-generation SRL therapy. Several symptoms and comorbidities associated with acromegaly improve in response to SRL therapy, including headache, soft tissue swelling, ventricular function, and sleep apnea.

Several factors have been reported as possible predictors of biochemical response to first-generation SRL therapy, including age and sex of the patient, baseline GH and IGF-1 levels, genetic abnormalities, histopathologic features, and imaging characteristics of the underlying tumor (Table 3).
In a study of 88 patients who were treated with lanreotide depot at maximal doses for 48 weeks, older age (odds ratio [OR], 2.2 per higher decade of life) and female sex (OR, 2.9) were associated with biochemical control of GH excess (normal serum IGF-1 and GH level below 2.5 μg/L).60 In the same study, lower serum IGF-1 levels at baseline were associated with a higher likelihood of achieving biochemical control.60 Lower serum GH levels at baseline have also been reported as being predictive of IGF-1 normalization in response to SRL therapy in some but not other studies.60,63

Germline genetic abnormalities are present in a minority of patients with acromegaly and may influence the response to first-generation SRL therapy.15 Patients with inactivating mutations in the aryl hydrocarbon receptor–interacting protein (AIP) gene who develop acromegaly have been reported to exhibit lower GH and IGF-1 decrements after SRL administration and are less likely to show tumor shrinkage on such therapy.64 In patients with AIP-mutated somatotroph adenomas, miR-34a is up-regulated and appears to promote resistance to SRL therapy.65 Patients with GPR101 gene amplification develop acrogigantism of early onset.66 These patients are unlikely to show IGF-1 normalization in response to SRL therapy.66 Patients with the McCune-Albright syndrome may also show a poor biochemical response to SRL therapy.67

Somatic (tumor) mutations in the GNAS gene (gsp) are present in 40% of somatotroph adenomas and may predict a more favorable GH response to SRL therapy in some but not all studies.68,69 In a meta-analysis, the presence of the gsp mutation was associated with a greater decrease in GH levels during the acute octreotide test (which predicts the response to long-term SRL therapy).68

Densely granulated adenomas account for 30% to 50% of somatotroph tumors and show perinuclear keratin immunoreactivity.70 These tumors are generally seen in older patients and are typically hypointense on T2-weighted MRI sequences.70 Patients with densely granulated adenomas are more likely to respond to first-generation SRL therapy.61,69,71 In a study of 40 patients

<p>| TABLE 3. Possible Predictors of Biochemical Response to Medical Therapy for Acromegaly |</p>
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<tr>
<th>Drug class (agents)</th>
<th>Factors associated with higher response</th>
<th>Factors associated with lower response</th>
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<tr>
<td>First-generation SRLs (octreotide acetate, octreotide LAR, lanreotide depot, oral octreotide)</td>
<td>Clinical: older age, female sex</td>
<td>Endocrine: higher GH or IGF-1 levels at baseline</td>
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<td>Genetic: somatic gsp mutation</td>
<td>Genetic: AIP gene mutation, GPR101 gene amplification, McCune-Albright syndrome</td>
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<td>Histologic/molecular markers: densely granulated tumors, higher SSTR2 expression, lower Ki-67 index, higher E-cadherin expression, higher ZAC1 expression, lower β-arrestin expression, higher RKIP expression</td>
<td>Histologic/molecular markers: higher SSTR5 expression, lower AIP expression</td>
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<td>Imaging characteristics: T2-hypointense tumors, higher maximal pixel intensity on image texture analysis</td>
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<tr>
<td>Second-generation SRL (pasireotide LAR)</td>
<td>Higher SSTR2 or SSTR5 expression</td>
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<td>Imaging characteristics: T2 signal intensity</td>
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<tr>
<td>Cabergoline</td>
<td>Lower baseline serum IGF-1</td>
<td>Diabetes mellitus</td>
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<td>Pegvisomant</td>
<td>Lower BMI</td>
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<td>Lower baseline serum IGF-1</td>
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BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor 1; LAR, long-acting release; RKIP, Raf kinase inhibitory protein; SRL, somatostatin receptor ligand; SSTR, somatostatin receptor.
who were treated with octreotide LAR for a mean of 28 months, those with densely granulated tumors were significantly more likely to normalize serum IGF-1 and GH levels (GH level <1 µg/L) in response to SRL administration (OR, 58.4) compared with those with sparsely granulated tumors.71

Several other histopathologic characteristics and molecular tumor markers have been proposed as possible predictors of response to SRL. Ki-67 is a nuclear protein expressed in cells that are not in resting phase (G0).70 A lower Ki-67 index (Ki-67 <2.3%) may predict a higher response to first-generation SRL therapy.82 In addition, a higher SSTR-2 expression has been associated with a greater likelihood of achieving biochemical control in patients with acromegaly in response to SRL therapy.51,72 A higher ratio between SSTR-2 and SSTR-5 expression has been associated with better biochemical response to first-generation SRL therapy.73 Among patients without germline AIP mutations, a higher AIP expression in somatotroph tumor cells has been associated with a higher likelihood of achieving biochemical control on first-generation SRL therapy.74 It has been suggested that SSTR-2 expression, AIP expression, and the Ki-67 index may independently predict the biochemical response to SRL therapy.72,74

A lower β-arrestin expression, a protein that downregulates SSTR-2–mediated signaling, has been associated with a higher response rate to SRL therapy.75 In addition, a higher expression of E-cadherin, a cell adhesion protein, has been associated with a greater likelihood of achieving biochemical control on SRL therapy.76 Similarly, a higher expression of ZAC1, a zinc finger transcription factor that appears to be one of the intracellular signaling mediators of octreotide action, has been associated with higher biochemical response to first-generation SRL therapy.77-79 A higher expression of Raf kinase inhibitory protein, which is involved in SSTR-mediated signaling, has been associated with a better response to SRL therapy in acromegaly.80

Image characteristics on MRI may also predict the response to first-generation SRL therapy. T2-hypointense adenomas account for about 40% of somatotroph adenomas and are generally densely granulated.81,82 Tumors that are T2 hypointense are more likely to show a good biochemical response to SRL therapy.81-83 Image texture analysis refers to quantification of image gray-level pixel distribution on MRI.84 In a recent study, maximum pixel intensity was predictive of serum IGF-1 normalization on first-generation SRL therapy.52

Pasireotide LAR is a second-generation SRL with expanded SSTR specificity (engaging SSTR-1, 2, 3, and 5).85 Pasireotide LAR is likely to be more effective than first-generation SRLs in effecting control of GH secretion.85 Approximately 20% of patients with acromegaly who are not controlled on first-generation SRLs can achieve biochemical control on pasireotide LAR therapy.86 Whether SSTR-5 or SSTR-2 expression predicts response to pasireotide LAR therapy is debatable.87,88 In addition, T2 signal intensity on MRI may predict the response to pasireotide LAR.89

All SRLs share similar potential for gastrointestinal adverse effects (diarrhea, abdominal pain, cholelithiasis), alopecia, and sinus bradycardia.38 However, pasireotide LAR is more likely than first-generation SRLs to induce hyperglycemia or diabetes mellitus, probably as a consequence of SSTR-5 activation that results in blunted insulin and incretin secretion.85,86

Cabergoline is a D2-selective agonist at dopamine receptors that is Food and Drug Administration approved for treatment of patients with hyperprolactinemia. It is used off-label in patients with acromegaly. A meta-analysis of 9 studies reported that cabergoline therapy (dose range, 0.3 to 7.0 mg/wk) resulted in IGF-1 normalization and GH control in, respectively, 34% and 48% of 149 patients.90 Lower baseline serum IGF-1 levels and previous radiation therapy to the sella predicted a good biochemical response to cabergoline therapy.90 In the same meta-analysis (5 studies) of data on patients inadequately controlled on SRLs, add-on cabergoline therapy resulted in IGF-1 normalization in 52% of 77 patients.90 Lower
baseline serum IGF-1 levels predicted a higher likelihood of biochemical response to cabergoline.90

Adverse effects associated with cabergoline therapy include nausea, vomiting, orthostatic dizziness, headache, nasal congestion, constipation, and digital vasospasm.90 In patients with Parkinson disease, cabergoline therapy in high doses (3 to 7 mg/d) has been associated with cardiac valvulopathy, probably as a result of activation of 5-hydroxytryptamine subtype 2B receptors by cabergoline.91 Cabergoline doses administered to patients with acromegaly are often above the usual dose range advised in hyperprolactinemic patients (0.5 to 2.0 mg/wk) but lower than typical doses used in Parkinson disease (3 to 7 mg/d). The risk of cardiac valvulopathy in patients with hyperprolactinemia appears to be low.92 However, the risk of valvulopathy in patients with acromegaly receiving cabergoline remains unclear. Periodic echocardiography appears prudent in patients receiving more than 2 mg/wk of cabergoline. Nonetheless, the cost-effectiveness of this strategy has not been established. Impulse control disorders have been reported in hyperprolactinemic patients receiving cabergoline therapy, presumably as a consequence of D2 receptor activation in the mesolimbic dopamine pathway.93

Pegvisomant is a GH analogue that carries several amino acid substitutions and functions as a GHR antagonist.94 Several polyethylene glycol moieties have been covalently attached to pegvisomant to prolong its half-life in the systemic circulation.94 Pegvisomant binds to the GHR with high affinity but does not activate downstream signaling through the JAK/STAT pathway.94 Pegvisomant is effective in inhibiting GH action, resulting in IGF-1 normalization in 89% to 97% of patients with acromegaly in pivotal clinical trials.95,96 In postmarketing studies, pegvisomant therapy led to IGF-1 normalization in up to 75% of patients.97 It is possible that inadequate dose titration or adherence to therapy may have resulted in lower effectiveness of pegvisomant in real-world settings. Glycemia may improve in patients switching from SRL therapy to pegvisomant as a consequence of inhibition of GH action and lack of suppression of insulin or incretin secretion.98 Patients with lower body mass index or lower serum IGF-1 levels at baseline appear to be more likely to achieve IGF-1 normalization with pegvisomant monotherapy.99 Patients with diabetes mellitus may be less likely to achieve IGF-1 normalization with pegvisomant, presumably reflecting the effects of insulin on GHR expression in hepatocytes.100 Pegvisomant has been administered as add-on therapy to patients who have a partial response to SRLs and is an effective treatment option in this population.101,102 Patients with lower body mass index or lower serum IGF-1 levels at baseline may require a lower pegvisomant dose to normalize serum IGF-1 with combination therapy.103

Adverse effects associated with pegvisomant administration include transaminitis, rash, and injection site reactions (including lipohypertrophy).95,104 Transaminitis is reversible with dose reduction or drug discontinuation and has not been reported to result in hepatic failure. A verified increase in size of somatotroph adenomas has been reported in 3.2% of 936 patients receiving pegvisomant therapy.104 In some cases, this increase in tumor size may have been a consequence of withdrawal from SRL therapy or may have simply reflected the natural history of more aggressive pituitary adenomas. Periodic pituitary imaging is advisable in patients who receive pegvisomant therapy to detect a possible increase in tumor size.

Several investigational therapies are currently in development, including paltusotine (an orally active, nonpeptide SRL), somatoprim (an SRL engaging SSTR-2, 4, and 5), CAM2029 (liquid crystal formulation of octreotide depot), and an antisense oligonucleotide targeting the mRNA encoding the GHR.105,106

Radiation Therapy
Radiation therapy is another treatment option for patients with acromegaly and is...
typically advised for those who are not in remission postoperatively and do not show a good response or tolerance to medical therapy. Radiation therapy may also be administered to control tumor growth in patients with pituitary adenomas that do not respond adequately to surgery and medical therapy. Radiation therapy can be administered either as conventional fractionated radiation therapy or, increasingly, as stereotactic radiation therapy (Gamma knife, linear accelerator/CyberKnife, and proton beam). Stereotactic radiation therapy can be delivered in a single session (“radiosurgery”) in patients with smaller tumors that are distant from the optic apparatus. Biochemical control can be achieved in up to 60% of patients with acromegaly after a period of several years, thus necessitating the institution of interim medical therapy until the salutary effects of radiation therapy occur. In a recent retrospective analysis of 352 patients from the German Acromegaly Registry, endocrine remission was achieved sooner among patients who received stereotactic radiosurgery in comparison with those who received fractionated radiotherapy (mean interval of 2 years vs 3 years). However, the proportion of patients who achieved endocrine remission at 10 years after radiation therapy was not different between the groups. Tumor control is achieved in more than 90% of patients with acromegaly receiving radiation therapy.

Adverse effects associated with radiation therapy include anterior hypopituitarism (affecting 40% to 50% of patients at 5 years) and optic or other cranial neuropathies (in 1% to 2% of patients). The development of anterior pituitary hormone deficiencies may be less frequent after the administration of stereotactic radiosurgery in comparison with fractionated techniques. Temporal lobe necrosis, stroke, and secondary tumors have been uncommonly reported in association with conventional radiation therapy. However, long-term data are needed to determine whether these uncommon, long-term adverse effects may also occur after stereotactic radiation therapy because newer radiotherapy techniques minimize the exposure of healthy brain structures to radiation.

CONCLUSION
A high index of suspicion is needed to minimize delays in diagnosis of acromegaly. Early diagnosis and adequate treatment of acromegaly are needed to mitigate excess mortality associated with this condition. Pituitary surgery is currently the cornerstone of management, with medical therapies and radiation therapy typically representing second- and third-line options, respectively.

Further advances in our understanding of the pathogenesis of somatotroph adenomas are needed and may eventually lead to the development of novel, rationally designed medical therapies. Prospective studies that use robust criteria to assess potential predictors of response to medical therapy will be helpful to refine our ability to reliably predict therapeutic responses. In the not too distant future, a robust, targeted approach to medical therapy in patients with acromegaly may become a reality.

**Abbreviations and Acronyms:** GH, growth hormone; GHR, growth hormone receptor; GHRH, growth hormone-releasing hormone; IGF-1, insulin-like growth factor 1; LAR, long-acting release; SRL, somatostatin receptor ligand; SSTR, somatostatin receptor; STAT, signal transducer and activator of transcription

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