Acromegaly

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Summary

Acromegaly is a rare, chronic, progressive disease characterized by an excess secretion of growth hormone (GH) and increased circulating insulin-like growth factor 1 (IGF-1) concentrations. It is caused by a pituitary adenoma in the vast majority of cases. The clinical diagnosis, based on symptoms related to GH excess, is often delayed due to the insidious nature of the disease. Consequently, patients often have established systemic complications at diagnosis with increased morbidity and premature mortality. Serum IGF-1 measurement is recommended as the initial screen for patients with suspected acromegaly. The gold standard diagnostic test remains the oral glucose tolerance test with concomitant GH measurement. Therapy for acromegaly is targeted at decreasing GH and IGF-1 levels, ameliorating patients’ symptoms and decreasing any local compressive effects of the pituitary adenoma. The therapeutic options for acromegaly include surgery, medical therapies (such as dopamine agonists, somatostatin receptor agonists and the GH receptor antagonist pegvisomant) and radiotherapy. A multidisciplinary approach is recommended with often a requirement for combined treatment modalities. With disease control, associated morbidity and mortality can be reduced. The recently published evidence-based guidelines by the Endocrine society addressed important clinical issues regarding the evaluation and management of acromegaly. This review discusses advances in our understanding of the pathophysiology of acromegaly, diagnosis of various forms of the disease and focuses on current treatment modalities, and on future pharmacological therapies for patients with acromegaly.

Background

Acromegaly is a slowly progressive disease caused by chronic hypersecretion of growth hormone (GH) and excess circulating insulin-like growth factor-1 (IGF-1). The etiology of acromegaly is almost invariably an underlying GH-secreting pituitary adenoma. Rarely, it is due to a hypothalamic tumor secreting GHRH or ectopic growth hormone releasing hormone (GHRH) secretion, or very rarely GH from an ectopic source.1 Acromegaly is rare with an estimated prevalence of 36-60 cases per million with an annual incidence of 3–4 per million.2

Pathophysiology

Pituitary tumors are monoclonal adenomas that account for ~10% of primary intracranial neoplasms.2 GH is synthesized and stored in somatotroph cells, which account for >50% of pituitary hormone secreting cells.3 GH production and secretion is regulated by hypothalamic GH-releasing hormone, ghrelin and somatostatin. IGF-1 inhibits GH secretion by both direct effect on the somatrophs and indirectly through stimulation of somatostatin that inhibits GH secretion. GH is secreted in sporadic pulses with minimal basal secretion
determined by sex, age, neurotransmitters, exercise and stress.

GH action is achieved via its interaction with a single-chain transmembrane glycoprotein receptor (GHR). The GH molecule interacts with a preformed dimer of identical GHR pairs, causing internalization of the receptor to initiate signaling. As a consequence, two Janus tyrosine kinase 2 molecules undergo autophosphorylation and in turn phosphorylate the GHR cytoplasmic domain. This activates intracellular proteins involved in signal transduction and transcription (STAT).5

The gene encoding the GHR is ubiquitously expressed, particularly in liver, fat and muscle. GH activation of the intracellular molecule STAT5b induces transcription of IGF-1. Systemic IGF-1 is synthesized primarily in the liver but also in extrahepatic tissues including bone, muscle and kidney and in the pituitary gland itself. IGF-1 circulates in serum bound to IGF-1 binding protein (IGFBP-3), or IGFBP-5, and acid-labile subunit in a 150-kD complex. Less than 1% of total serum IGF-1 circulates as a free hormone. The IGF-1 cellular effects are mediated by the IGF-1 receptor (IGF-1R), a heterotetrameric protein structurally similar to the insulin receptor. IGF-1 acts to mediate tissue growth or locally synthesized IGF-1 acts in a paracrine manner to regulate local GH target tissue growth. 6

Several candidate genes that could account for the somatotroph clonal expansion have been examined in animal models. These include the retinoblastoma tumor suppression gene and p27. Disruption of the MENIN gene, results in multiple endocrine neoplasia type I. Ras mutations have been reported to activate GH secretion in experimental animal models, as have mutations of a pituitary tumor-transforming gene. Mutations in the tumor suppressor gene, arylhydrocarbon receptor interacting protein (AIP), are prevalent in young-onset, GH excess patients and familial isolated and young-onset pituitary adenomas. In a longitudinal, international, collaborative study, Korbonits et al.7 identified AIP mutations in 46.7% of patients with gigantism in their cohort of 216 patients. Two histological subtypes of GH-secreting pituitary adenoma have been identified based on the pattern of cytoplasmic cytokeratin. Sparsely granulate cytokeratin at histology suggest more invasive lesions. These lesions are more common in younger patients and are less response to somatostatin receptor ligand therapy. 8

Clinical features

First observed by Verga in 1864, acromegaly is characterized by disproportionate skeletal, tissue and organ growth. At diagnosis, patients may exhibit a spectrum of clinical signs including skeletal and acral overgrowth and soft tissue enlargement with frontal bossing, mandibular prognathism, jaw malocclusion and overbite, skin thickening, and increased ring and shoe size (Table 1). Other features include hyperhidrosis, paresthesia, goiter, arthritis, kyphoscoliosis, headaches, visual field deficits, colon polyps, sleep apnea and daytime somnolence, reproductive disorders and cardiovascular disease. 9 It should be highlighted that there is a large spectrum of clinical features associated with acromegaly and patients may have a spectrum of mild to severe clinical phenotype; therefore, a high index of suspicion is required.

Morbidity

Acromegaly often evades diagnosis until in its clinically obvious later stages, often resulting in a delay of 5–10 years after approximate symptom onset. 10 Patients often present with significant co-morbidities including hypertension, diabetes mellitus and sleep apnea.

Arterial hypertension is reported to affect up to 40% of patients with acromegaly. Experimental and clinical studies have shown that both GH and IGF-1 exert direct effects on myocardial growth and function. The key feature of acromegaly cardiomyopathy is concentric biventricular hypertrophy. Hypertrophy involves proliferation of the myocardial fibrous tissue, which results in interstitial remodeling and subsequent impaired ventricular relaxation and diastolic dysfunction. The cardiomyopathy of acromegaly is further aggravated by hypertension and glucose abnormalities.

Valvular heart disease and arrhythmias are more frequently observed in patients with acromegaly, with up to 40% of patients suffering from conduction disorders. Colao et al.6 demonstrated a high prevalence of both mitral and aortic valve dysfunction in patients with active acromegaly. If the disease is uncontrolled, then diastolic and ultimately systolic heart failure can develop.

Impaired glucose tolerance and diabetes mellitus are frequently associated with acromegaly as GH excess promotes insulin resistance, in the liver and the periphery. Hyperinsulinaemia and increased gluconeogenesis are observed in patients

<table>
<thead>
<tr>
<th>Table 1. Clinical features of acromegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct tumor effects</strong></td>
</tr>
<tr>
<td>Visual field deficit</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Hypopituitarism</td>
</tr>
<tr>
<td><strong>Soft tissue and skin changes</strong></td>
</tr>
<tr>
<td>Increased skin thickness and soft tissue hyperplasia</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Skin tags and acanthosis nigricans</td>
</tr>
<tr>
<td><strong>Bone and joint features</strong></td>
</tr>
<tr>
<td>Somatic effects (Acral enlargement, prognathism, frontal bossing)</td>
</tr>
<tr>
<td>Arthropathy/osteoarthritis</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Osteopenia, vertebral fractures</td>
</tr>
<tr>
<td>Proximal myopathy</td>
</tr>
<tr>
<td>Hearing loss</td>
</tr>
<tr>
<td><strong>Cardiovascular features</strong></td>
</tr>
<tr>
<td>Biventricular hypertrophy</td>
</tr>
<tr>
<td>Increased interventricular septum thickness (eccentric hypertrophy)</td>
</tr>
<tr>
<td>Diastolic dysfunction at rest and/or systolic dysfunction on effort</td>
</tr>
<tr>
<td>Diastolic heart failure</td>
</tr>
<tr>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Endothelial dysfunction and increased carotid IMT</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
</tr>
<tr>
<td><strong>Metabolic features</strong></td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Reduced total cholesterol and increased triglycerides</td>
</tr>
<tr>
<td>Increased nitrogen retention</td>
</tr>
<tr>
<td><strong>Respiratory features</strong></td>
</tr>
<tr>
<td>Upper airway obstruction</td>
</tr>
<tr>
<td><strong>Signs of acromegaly</strong></td>
</tr>
<tr>
<td>Macroglossia</td>
</tr>
<tr>
<td>Sleep apnea</td>
</tr>
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with acromegaly. The exact prevalence of overt diabetes mellitus in acromegaly is unknown, but ranges from 19% to as high as 52%. The differing prevalence rates are likely due to the heterogeneity of the case series, in addition to the impact of revised accepted criteria for the diagnosis and classification of diabetes mellitus.

Respiratory disorders can develop in patients with acromegaly, as a result of anatomical changes affecting craniofacial bone and soft tissues, as well as alterations in activity of respiratory muscles. Sleep apnea can affect up to 60% of patients, most often due macrognosia and anatomical narrowing of the upper airways. Central sleep apnea has been observed in a minority of cases.

Arthropathy affects ~75% of patients with acromegaly and is the leading cause of morbidity and functional disability for these patients. Pain is the most common symptom, usually exacerbated by activity. Carpal tunnel syndrome is present in up to 64% of patients at presentation. With disease progression the bone undergoes accelerated turnover and the articular cartilage thins with narrowing of joint spaces, similar to features of osteoarthritis. A recent meta-analysis, observed a higher bone formation, but with a greater frequency of vertebral fractures compared with controls.

In recent years, particular focus has been placed on colorectal cancer (CRC) to a lesser extent on breast, prostate and thyroid cancer rates in patients with acromegaly. The pooled odd ratios are increased for benign neoplasia (2.48 for colonic adenomas and 3.557 for hyperplastic polyps), in addition to colon cancer (2.04–4.351). Orme et al. investigated the incidence and mortality for cancer in a cohort of 1239 patients. They excluded all malignancies pre-diagnosed to the diagnosis of acromegaly and used reliable national cancer registers for cross-examination. The overall cancer incidence was lower in the acromegaly patients than in the normal population (79 vs. 109 malignancies, respectively). However, the SIRs revealed a small increase in colon cancers in acromegaly patients (SIR 1.68), and the death rate from colon cancer outnumbered that recorded in the normal population (13 observed deaths vs. 5 expected). The occurrence of cancer was unrelated to either disease duration or age at diagnosis but the standard mortality rate associated with cancer was higher with post-treatment levels of GH > 10 µg/l.

More recent results from the German Acromegaly Registry for 446 patients (6656 person-years from diagnosis) did not show any evidence for a higher incidence of cancer (SIR 0.75, 95%CI 0.55–1.0), most notably CRC or breast cancer.

**Mortality**

It is well reported in the literature that untreated acromegaly is associated with reduced life expectancy. Analysis of the determinants of mortality indicate that ~60% die from cardiovascular disease, 25% from respiratory disease and 15% from malignancies. With advances in the medical therapy, surgical techniques and localized stereotactic radiotherapy, overall mortality rates in acromegaly have improved. Although mortality in acromegalic patients remains elevated compared with the general population in several studies, the mortality increase is generally less than 2-fold, compared with the 2- to 3-fold mortality rates seen in earlier series.

There is compelling evidence to support that the last available follow-up GH value is the most predictive survival index. Bates et al. reported that in a cohort of 79 patients with acromegaly, the Standardised Mortality ratio (SMR) fell from 2.6 to 2.0 if treatment reduced GH levels to under 10 mU/l (5 µg/l). Even more significant was the fact that mortality was reduced to normal if post-treatment GH levels of <5 mU/l (2.5 µg/l) were achieved. In the West Midlands Acromegaly Study, comparison of crude death rates per 1000 population suggested that a GH of 2 µg/l may be a more appropriate treatment target with a step-up in the death rate once GH exceeded 2 µg/l. The Finnish Nationwide Survey of Mortality in Acromegaly reported similar findings. In a cohort of 334 acromegalic patients with 56 deaths, excess mortality was seen in those with post-treatment GH levels =2.5 µg/l (SMR, 1.63 (1.1–2.35); P < 0.001).

In a recent meta-analysis, Holdaway et al. focused on the relationship between biochemical measurements and mortality during follow-up after treatment for acromegaly. Mortality was close to the expected level when last available GH was under 2.5 µg/l (SMR, 1.1; 95% CI, 0.9–1.4), whereas the SMR for those with elevated IGF-1 at last follow-up remained significantly increased (SMR, 2.5; 95% CI, 1.6–4.0). However, it should be noted that two of the largest studies in the meta-analysis, comprising a total of 151 deaths in 753 patients, have failed to demonstrate any relationship between post-treatment IGF-1 levels and mortality (Relative Risk, 1.2; 95% CI, 0.7–2.2; P = 0.26).

Therefore, the biochemical aim of treatment in acromegaly should be reduction of GH values to <0.5 µg/l and possibly even lower to <1 µg/l, although care must be taken that this is not at the expense of inducing GH deficiency and hypopituitarism, which in itself is associated with an adverse outcome.

The introduction of GH antagonists as medical treatment for acromegaly necessitates the use of IGF-1 in the biochemical monitoring of patients treated with these agents. Holdaway et al. found that those with normal IGF-1 had mortality close to the expected values for the general population (SMR, 1.1; 95% CI, 0.9–1.4), whereas the SMR for those with elevated IGF-1 at last follow-up remained significantly increased (SMR, 2.5; 95% CI, 1.6–4.0). However, it should be noted that two of the largest studies in the meta-analysis, comprising a total of 151 deaths in 753 patients, have failed to demonstrate any relationship between post-treatment IGF-1 levels and mortality (Relative Risk, 1.2; 95% CI, 0.7–2.2; P = 0.26). Therefore, the biochemical aim of treatment in acromegaly should be reduction of GH values to <0.5 µg/l and possibly even lower to <1 µg/l, although care must be taken that this is not at the expense of inducing GH deficiency and hypopituitarism, which in itself is associated with an adverse outcome.

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Although hypopituitarism is associated with increased mortality, first identified by Rosen and Bengtsson, there is little data on the role of hypopituitarism in patients with acromegaly. In the West Midlands study, there was a trend (P = 0.07) toward reduced survival in patients with acromegaly who had a greater number of deficient hypothalamo-pituitary axes compared with those without evidence of hypopituitarism. Sherlock et al. showed that neither TSH deficiency nor gonadotropin deficiency was associated with increased mortality in acromegaly.
on internal analysis (gonadotropin deficiency was associated with increased SMR compared with the general population); however, adrenocorticotropic hormone (ACTH) deficiency was associated with increased mortality [RR, 1.7 (95% CI, 1.2–2.5); \( P = 0.004 \)]. The cause of death was predominantly cardiovascular, and higher doses of hydrocortisone therapy were associated with increased mortality.20

Other variables found to influence outcome included hypertension, duration of the disorder before treatment and age. Hypertension and glucose intolerance are important contributory factors to the vascular morbidity associated with acromegaly. However, there are few published reports on their impact on mortality in acromegaly and how this correlates with GH and IGF-1 levels. Hypertension is considered one of the most relevant negative prognostic factors for mortality in acromegaly.

Diagnosis

The diagnosis of acromegaly is based upon a combination of clinical examination and biochemical demonstration of dysregulated autonomous GH secretion as well as elevated IGF-1 levels. Serum GH concentrations are typically elevated but levels may fluctuate widely. Measuring serum IGFI-1 in a patient with clinically suspected acromegaly should be the initial test.26 It is also recommended to test patients without the typical clinical appearance but who have associated comorbidities: sleep apnea, type 2 diabetes, disabling arthritis, carpal tunnel syndrome, hyperhidrosis and hypertension. A normal IGF-1 level (using age- and sex-matched reference ranges) effectively excludes the diagnosis of acromegaly. False positives may occur in pregnancy, patients taking estrogen therapy and late-stage adolescence. Multiple factors can make the biochemical interpretation of IGF-1 level challenging, including the presence of certain pathological conditions such as hepatic and renal failure, malnutrition, hypothyroidism and uncontrolled hyperglycemia.

Failure of normal suppression of serum GH following a standard 75g-oral glucose load remains the gold-standard diagnostic test and should be used to confirm the diagnosis in all cases with high or equivocal IGFI-1 or in the presence of conditions interfering with the measurement where clinical suspicion is high.27

The use of higher sensitivity immunofluorometric, chemiluminescent and immunoradiometric assays has been associated with significantly lower nadir GH during oral glucose tolerance test (OGTT) in healthy controls than was previously thought (ranging from 0.029–0.25 mg/l), with a gender difference noted in some studies.27 As ultrasensitive immunoassays are not uniformly available worldwide, current guidelines suggest a cutoff for nadir GH after OGTT < 1 µg/l acceptable for exclusion of the diagnosis.28 It should be highlighted that this could result in inaccurate exclusion of mild active disease. A further challenge in diagnosis is the presence of discordant serum GH and IGF-1 levels. Elevated IGFI-1 with normal GH may reflect early disease and should warrant further investigation (including imaging) to clarify the diagnosis.28

Current guidelines recommend contrast-enhanced pituitary MRI as the first line imaging modality, after biochemical confirmation of acromegaly. If MRI is contraindicated or unavailable then pituitary computed tomography should be performed. At diagnosis, macroadenomas are detected in 73% of patients.2

Visual field testing is recommended in all patients with confirmed pituitary tumors. As onset is often insidious, patients may not be aware of any alteration in their vision and a baseline assessment facilitates accurate interpretation of further testing if a deterioration is reported by the patient or in response to therapy.

Assessment of the integrity of the other pituitary hormones by the combination of basal and appropriate dynamic testing is recommended. Hyperprolactinemia from tumor co-secretion occurs in up to a third of patients and can contribute to hypogonadism, but may also occur a result of ‘stalk effect’ due to tumor compression of the pituitary stalk interrupting the delivery of inhibitory dopamine to the pituitary.29 Evaluating all patients with acromegaly for associated co-morbidities is recommended at diagnosis (Table 2), in addition to longitudinal monitoring during follow-up.26

Treatment

Treatment goals in acromegaly include symptom relief, tumor control with maintenance of pituitary function, biochemical normalization of GH/IGF-1 and reversal of the excess morbidity and mortality associated with the disorder. Current modalities of treatment available include: surgery, medical therapy and radiotherapy. Treatment is complex and frequently more than one modality is required to achieve treatment goals. The decision to treat and the therapeutic intervention used is based on a number of factors, which need to be weighed and tailored carefully for each patient in a multidisciplinary setting.

The definition of biochemical remission is difficult due to variability in the assay and reference ranges used. It is crucial that the same GH and IGF-1 assay is maintained in the same patient throughout their management. While it remains controversial, the current recommended biochemical target is a random GH < 1 µg/l.26 The decline in IGF-1 is more delayed compared with GH, likely due to differential half-life of IGF-binding proteins. IGF-1 levels measured at 12 weeks after surgery are a valid reflection of surgical remission. If the IGF-1 level has declined but is still not normal, measurement of a repeat IGF-1 level is warranted due to variability in the IGF-1 assay.

A normal IGF-1 value and undetectable GH value are sufficient for indicating surgical remission. However, if the GH is detectable (i.e. >0.4 µg/l), measurement of GH after a glucose load may yield important information. The mean value of several samples taken a few hours apart throughout the day can also be used (GH day curve (GDH)) as it is significantly correlated with the GH nadir during OGTT and with the IGF-1 level.30 While the ideal endocrine outcome of any therapy in acromegaly is a normal IGF-1 value and undetectable GH value, levels that are associated with a normalization of mortality (as discussed in the section above relating to mortality) are acceptable.

Surgery

Transphenoidal surgery by an experienced pituitary surgeon is the initial treatment of choice recommended for the majority of patients.26 Ninety percent of patients who undergo pituitary surgery are treated using the transphenoidal approach; craniotomy is rarely performed. The development of endoscopic and microsurgical transphenoidal surgery offers further advantages over the conventional techniques including the possibility of superior tumor clearance in previously difficult to access areas, less surgical morbidity, fewer complications and reduced postoperative pain.31

The main postoperative complaints relate to the transphenoidal approach including nasal congestion, sinusitis and...
Medical treatment

Medical therapy has an important role as an adjunctive treatment option for persistent disease following non-curative surgery and also as first line therapy where surgery is not a feasible therapeutic option. Consensus guidelines outline the recommended role of medical therapy in the treatment of patients with acromegaly. There are a number of options for medical therapy in acromegaly, including somatostatin receptor ligands, GH receptor antagonists and dopamine agonists.

Somatostatin receptor ligands

Somatostatin is distributed throughout the nervous system and exerts neural control over many physiological functions, including the inhibition of GH release. It exists in two biologically active molecular forms: somatostatin-14 and somatostatin-28, with a short half-life of 2–3 min. Its action is mediated through G-protein coupled cell-surface receptors identified in a variety of tissues, including the pituitary. Both bioactive forms have high binding affinity toward all five identified receptor subtypes, SSR1-SSR5.40 GH-secreting pituitary adenomas express predominantly SSR2 and SSR5. First generation somatostatin analogs, octreotide and lanreotide, show high affinity binding to SSR2, and to a lesser extent to SSR5.41

Currently three long-acting SRL formulations are available, octreotide LAR, Lanreotide depot/autogel and pasireotide. Rapid acting subcutaneous octreotide is also available, and is administered two-three times daily. The long-acting octreotide LAR is administered intramuscularly every 4–6 weeks. The approved starting octreotide LAR dose is 20 mg monthly, with dose titration every 3–6 months to a maximum dose of 40 mg monthly. Lanreotide is available in a microsphere formulation (depot) injected intramuscularly every 7–14 days and an aqueous solution (Autogel) administered by deep subcutaneous injection every 4–6 weeks. For lanreotide autogel/depot, the approved starting...
dose is 90 mg monthly, with a maximum dose up to 120 mg monthly. A large body of evidence supports the efficacy of long-acting SRL therapy. In a critical analysis of the largest studies, octreotide LAR reduced GH to <2.5 μg/L and normalized the IGF-1 levels in 66 and 63%, respectively. Similar targets were achieved with lanreotide-SR in 52 and 47% of cases respectively. An earlier meta-analysis by Freda et al. reported the overall chance of IGF-1 normalization was 67% with octreotide and 47% with lanreotide SR. The higher efficacy reported with octreotide may be accounted by pre-selection of responsive cases (patients who showed response to short acting octreotide only being recruited to studies), inclusion of both primary and secondary therapy cases, and small case series. An inherent challenge to meta-analyses in such a complex condition is the lack of standardization of GH and IGF-1 assays, making comparison of absolute values between studies impossible.

Smaller tumors, lower baseline GH and IGF-1 levels, high SSR2 and SSR5 expression and those previously treated with surgery, are associated with a better response to SRL treatment. Routine performance of somatostatin receptor scintigraphy or an acute GH response to a subcutaneous octreotide injection as a determinant of SRL response, are not recommended.

Somatostatin receptor ligands also have proven efficacy in tumor volume reduction. This has been extensively reviewed recently by Colao et al. Tumor reduction may be mediated by direct anti-proliferative effects via activation of somatostatin receptors, or indirectly through angiogenesis inhibition. Sathiyapalan et al. showed a significant reduction in the functional vascularity of pituitary tumors in a small study of five patients after 24 weeks of octreotide therapy.

Published meta-analysis revealed that octreotide LAR and lanreotide formulation induce tumor shrinkage in 66.0 and 32.8% of cases, respectively. Tumor reduction is progressive with prolonged treatment, and decreased IGF-1 levels may be its best predictor, followed by age and degree of GH decrease.

A recent detailed review of published studies evaluating somatostatin analogues as first line therapy showed that 6-24 months of octreotide LAR therapy achieved >20-30% tumor volume reduction in 73-85% of patients. Unlike surgery, primary medical therapy cannot cure acromegaly. Based on a recent meta-analysis of available studies, primary SRL therapy is associated with a lower remission rates compared to initial surgery (45% vs. 67%). However, the accuracy of these remission rates is questionable given the non-comparable nature and the heterogeneity of studies included. Primary SRL therapy can be offered before surgery in patients with contraindications, in cases with unresectable tumor, or with severe comorbidities.

During SRL treatment, the most frequent side effects include abdominal discomfort, flatulence, cramps and diarrhea. Gallbladder sludge or gallstones occur in ~25% of subjects but are usually asymptomatic. SRL treatment was initially thought to aggravate the increased risk of glucose intolerance in these patients but the overall effect on glucose metabolism is not clinically significant.

Pasireotide is a multireceptor-targeted somatostatin receptor ligand, which has higher functional activity than octreotide on SSR subtypes except type 4, but in particular SSR5. In a large phase III randomized trial in patients with acromegaly, who were naive to medical therapy, pasireotide LAR and octreotide LAR have a similar effect of tumor reduction despite the fact that pasireotide was superior to octreotide in providing biochemical control. After 12 months of treatment, 81% of pasireotide patients had ≥20% reduction in tumor volume, compared with 77% of octreotide LAR patients. Pasireotide has similar rates of gastrointestinal side effects to other SRLs; however, the rates of hyperglycemia are significantly higher (occurring in 31–57% of patients).

**Pegvisomant**

Pegvisomant is a pegylated recombinant analog of human GH, incorporating nine amino acid mutations. PEGylation extends the half-life by reducing renal clearance. The mutations result in increased affinity to the GH receptor, in addition to blocking the second binding site on the receptor, preventing GHR dimerization and signal transduction. GH hypersecretion persists, as it does not target the GH secreting tumor at the level of the pituitary hence GH measurements cannot be used to monitor disease activity, and IGF-1 becomes the sole marker to monitor biochemical response during therapy.

Pegvisomant has been shown to be highly effective in providing biochemical control of acromegaly in multiple studies. In a 12-week double-blind placebo-controlled study, Trainer et al. randomly assigned patients to receive placebo, 10, 15, or 20 mg of pegvisomant. Normalization of IGF-1 (using age and sex-matched reference ranges) was achieved in 10%, 54%, 81% and 89%, respectively. Symptom control was also observed. The efficacy of pegvisomant over a longer period was subsequently studied. Van der Lely et al. reported 97% of patients achieving normal IGF-1 levels in patients receiving therapy for 12 months or more (Figure 1). Dose reduction was required in 11/90 patients as IGF-1 levels dropped below normal reference range for age and sex.

As mentioned above, pegvisomant does not exert a central effect on pituitary GH secretion; hence, fears exist over the possibility of increased tumor growth. The German Pegvisomant Observational Study is a multicenter surveillance study commenced in 2004 to assess the efficacy and safety of pegvisomant therapy in patients with acromegaly. Neuroradiological monitoring of tumor extension is performed with MRI imaging. Buchfelder et al. studied 3 years of follow-up data of 307 patients. Tumor progression was reported in between 2 and 3% of patients treated, an increase not outside the expected rate in patients not treated with pegvisomant.

Pegvisomant is administered as daily subcutaneous injection. It is generally well tolerated with adverse effects reported in <10% of patients. These may include injection site reactions with reversible lipohypertrophy and deranged liver function tests (attributable to the polyethylene glycol pegylated vehicle).

The predominant limiting factor for use of this agent in clinical practice remains its considerable cost. It is most often used as a second line agent in cases resistant or intolerant to SRL therapy or in combination with SRL’s in partially resistant cases. It is also a potential treatment option in acromegaly patients with difficult to control diabetes mellitus due to its favorable effect on glycemic control.

**Dopamine agonists**

Dopamine agonists bind to the D2 dopamine receptors in the pituitary gland and suppress prolactin and GH secretion. The use of bromocriptine, a first-generation dopamine agonist, is limited by its side effect profile including GI symptoms, lethargy and orthostatic hypotension. It also compares poorly with somatostatin receptor ligands in terms of efficacy with normalization of GH/IGF-1 reported in only 10% of patients.
Cabergoline, an ergot derivative dopamine agonist has been used for decades in the treatment of hyperprolactinaemia and Parkinson’s disease. Cabergoline is better tolerated and more effective than bromocriptine; however, its use was superseded by the development of SRL therapy showing higher efficacy rates.

Clinical trials of cabergoline in acromegaly are small, non-randomized and report variable results. In a recent systematic review of 10 trials with a total of 150 acromegaly patients, control of acromegaly was achieved in 34% of patients who received cabergoline therapy alone and 52% when added to SRL therapy in patients with suboptimal control. Consequently current guidelines recommend the use of cabergoline in patients with inadequate response to other medical treatment, with highest benefit expected in cases with modest persistent hormonal elevations. Conflicting data exists as to whether the co-secretion of prolactin is predictive of response to dopamine agonist therapy. Some studies conclude that tumors that co-secrete prolactin and GH have a greater response to dopamine agonist therapy, than those than solely secrete GH whereas others show no effect. There remains little data available regarding tumor shrinkage in patients with acromegaly who are receiving dopamine agonist therapy. Jaffe et al. reported combined results from a number of studies which revealed that 29% of patients had some tumor shrinkage on dopamine agonist therapy and the majority of patients who had tumor shrinkage were also hyperprolactinemic. It is difficult to interpret these finding given the small number and heterogeneous characteristics of the patients included.

The most frequent adverse effects of dopamine agonist therapy are nausea, constipation, headache, mood disturbance, nasal stuffiness and dizziness. Cardiac valve abnormalities were described with high doses of cabergoline used in Parkinson’s disease but not with current recommended dosage used for patients with acromegaly.

Dopastatin/BIM-23A760 is a chimeric molecule, has been shown in vitro to have high affinity for both somatostatin receptor subtypes- 2 and 5, in addition to dopamine 2 receptor. With increasing knowledge of the importance of SSR5 in regulation of GH in GH-secreting adenomas, dopastatin is undergoing further development in clinical studies to determine if there is a role for these compounds in the treatment of acromegaly.

Radiotherapy

Radiation therapy is used as adjuvant treatment in the setting of persistent disease despite surgery and/or medical treatment or if medical therapy is unavailable, unsuccessful or not tolerated. Radiotherapy has been shown to be effective in lowering serum GH levels but conflicting results have been reported regarding the normalization of IGF-1 levels. Furthermore, the delay in therapeutic benefit and the high risk of developing hypopituitarism, serve as arguments against the more routine use of radiotherapy.

Conventional radiotherapy has been used for >30 years in the adjunctive treatment of pituitary adenomas. It is generally delivered in fractionated doses, 4–5 times per week so as to reduce daily-fractionated dose. The risk of adverse effects being proportional to maximal dose per day. Early studies of conventional radiotherapy reported high efficacy rate of 80–100% however remission was defined as a GH level below 5-10 ng/ml. More recent studies using revised biochemical remission targets, report a mean remission rate between 50 and 60%. Jenkins et al. assessed the effects of conventional pituitary irradiation in 884 patients of the UK National Acromegaly Register. Mean GH levels declined from 13.5 to 5.3 ng/ml at 2 years after surgery, to 2 ng/ml by 10 years, and a further decline to 1.1 ng/ml at 20 years (Figure 2). Furthermore they observed a parallel fall in IGF-
1 levels with 63% of patients having a normal level by 10 years.64

Stereoactive radiotherapy offers improvement in immobilization, imaging and treatment delivery from conventional techniques. It can be delivered as a single fraction radiosurgery using a Gamma knife (a source of cobalt) or a linear accelerator or a stereoactive conformal radiotherapy delivered as fractionated treatment using a linear accelerator. There is no clear advantage for either of the radiosurgical techniques in terms of sparing normal tissue receiving high doses of radiation.65 A critical analysis of the literature reported variable rates of both biochemical and tumor response: 17–82% and 37–100% respectively.66 The authors attributed the wide variability to the use of different treatment schedules and definitions of remission.

Hypopituitarism is less frequent with radiosurgery than conventional radiotherapy. At least 50% of patient treated with conventional radiotherapy will have acquired new anterior pituitary hormonal deficits at 10 years.67 In cohorts treated solely with stereoactive techniques, rates of hypopituitarism vary between 0 and 20%.68 However, it is likely that the candidates for stereoactive radiotherapy had smaller remnants of disease and therefore less normal tissue irradiated.

Annual hormonal testing is required due to the risk of late hypopituitarism.26 Other complications following radiotherapy include the risk of second brain tumors, stroke, and rarely optic neuropathy, cranial nerve deficits and radionecrosis, a rare adverse effect of Gamma knife radiotherapy.69–71

Patients treated with conventional radiotherapy have been reported to have increased mortality predominantly due to stroke, independent of GH/IGF-I levels and hypopituitarism.72 Current guidelines recommend the use of stereoactive radiotherapy over conventional radiation therapy, unless significant residual tumor burden, or the lesion is too close to the optic chiasm.26

**Conclusion**

Prolonged exposure to elevated endogenous levels of GH and IGF-I results in a multisystem disease characterized by somatic overgrowth, multiple co-morbidities and premature mortality. Early detection prevents the development of irreversible complications of the disease, including cardiomyopathy, respiratory dysfunction, and arthropathy. Despite the imprecision of assays for GH and IGF-I, it is clear from epidemiologic studies that tight biochemical control is essential to reduce morbidity, control symptoms and improve mortality rates.

Optimal implementation of current guidelines in routine clinical practice and maximal use of the medical treatment could improve the long-term control of patients with significant benefits for morbidity and mortality. Another important aspect in the treatment of patients with acromegaly is also the appropriate targeted treatment of co-morbidities associated with acromegaly.

Achievement of the criteria for cure during or after therapy is determined by assessing biochemical control, targeting controlled levels of GH and normalization of IGF-I levels, monitoring tumor size, assessing residual pituitary function and monitoring co-morbidities.

New therapeutic molecules currently in trials will hopefully offer further benefit to those patients resistant to current therapeutic modes for this chronic progressive disorder.

**Conflict of interest:** None declared.

**References**