Acromegaly – An Update on Clinical Approach and Management

a report by
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Acromegaly is an uncommon disorder, with an annual incidence of three to four cases per million.[1,2] It is characterised by excessive secretion of growth hormone (GH), resulting in exaggerated growth of bone and soft tissues, multisystem involvement with multiple co-morbidities and heightened risk of premature mortality. GH is produced by the somatotroph cells of the pituitary gland in a pulsatile fashion. Circulating GH stimulates hepatic secretion of insulin-like growth factor-1 (IGF-1). More than 90% of cases of acromegaly are due to an adenomatous growth of the pituitary somatotroph cells. Both GH and IGF-1 circulate, and are responsible for the exaggerated somatic growth and metabolic derangements characteristic of this disease. Somatotroph adenomas usually occur in a sporadic fashion, but uncommonly can be part of a familial multiple endocrine neoplasia (MEN-1) syndrome associated with parathyroid and pancreatic disease, or as isolated, familial acromegaly. There are several effective treatment modalities to control this disorder and reduce or prevent the associated morbidity and mortality. This article reviews the clinical approach to acromegaly and highlights the therapies currently available.

Clinical Presentation

Men and women are affected equally by this disease and are diagnosed at a mean age of 40 years. Signs and symptoms of acromegaly are attributable either to GH hypersecretion or to localised mass effects of the tumour itself. The classic features of GH excess include frontal bossing, enlarged lips and nose, prognathic jaw, increased spacing of the teeth, enlarged tongue, changes in voice, oily skin or excess acne and enlarged hands and feet. Other than menstrual irregularities in women, most patients with acromegaly do not present with complaints or symptoms of somatic overgrowth. Rather, acromegaly is most commonly detected incidentally. Due to the fact that acromegaly is an insidious disease, it can go undetected for a decade or more prior to diagnosis. Therefore, GH-secreting pituitary adenomas are generally greater than 1cm (macroadenoma) at the time of initial presentation and frequently cause multiple systemic co-morbidities resulting from chronic GH excess. GH hypersecretion is associated with carpal tunnel syndrome, type 2 diabetes mellitus, obstructive sleep apnoea, headache and painful joint destruction. Cardiovascular (CV) abnormalities include hypertension, atherosclerosis, GH-mediated myocardial hypertrophy and diastolic and – in later stages – systolic dysfunction. Control of GH hypersecretion and normalisation of IGF-1 can dramatically improve these medical co-morbidities. Signs and symptoms of local tumour invasion include headache, visual compromise due to involvement of the optic chiasm or cavernous sinuses or hypopituitarism due to compression of the normal gland.

Retrospective studies have suggested an increased incidence of malignancy in patients with acromegaly, particularly of the colon.[3]

These findings are controversial and have not been clearly demonstrated in other studies. In a recent case-control study, the prevalence of colorectal hyperplastic polyps was significantly higher in patients with acromegaly compared with controls.[4] Whether the risk of colon cancer and/or polyps is improved with biochemical control is unknown. A baseline screening colonoscopy to exclude colon cancer may be warranted in patients with acromegaly.

Untreated, acromegaly causes an approximate two- to four-fold increase in mortality, primarily due to CV complications.[1] In a recent meta-analysis, acromegaly was associated with a mean standardised mortality ratio of 1.62 compared with a normal population.[5] In this study, biochemical cure following surgery was associated with a residual 10% increased mortality risk, although the authors note that this analysis should be interpreted with caution as it is based on a small number of studies and did not take into account treatment modalities in addition to surgery. Other studies have demonstrated that biochemical normalisation is associated with a mortality risk similar to that of the general population.[6]

Biochemical control is associated with an improvement in glucose tolerance and symptoms related to soft-tissue overgrowth; however, bony abnormalities usually do not regress.[7] In a recent study of subjects with acromegaly and obstructive sleep apnoea, the latter resolved in all patients after surgical cure.[8] Other studies have suggested that sleep apnoea may improve, but not always resolve, following biochemical normalisation. Other CV risk factors – including diastolic function – are likely to improve as well.[9] Therefore, control of acromegaly has critical implications with regard to preventing the long-term medical and mortality consequences of the disease.
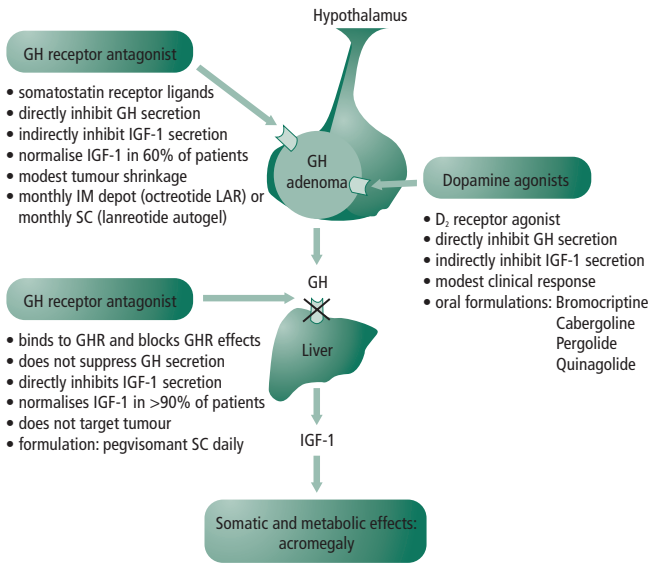
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Figure 1: Medical Options for the Treatment of Acromegaly

GH receptor antagonist
- somatostatin receptor ligands
- directly inhibit GH secretion
- indirectly inhibit IGF-1 secretion
- normalise IGF-1 in 60% of patients
- modest tumour shrinkage
- monthly IM depot (octreotide LAR) or monthly SC (lanreotide autogel)

Hypothalamus

GH adenoma

Dopamine agonists
- D$_2$ receptor agonist
- directly inhibit GH secretion
- indirectly inhibit IGF-1 secretion
- modest clinical response
- oral formulations: Bromocriptine
  Cabergoline
  Pergolide
  Quinagolide

GH receptor antagonist
- binds to GHR and blocks GHR effects
- does not suppress GH secretion
- directly inhibits IGF-1 secretion
- normalises IGF-1 in >90% of patients
- does not target tumour
- formulation: pegvisomant SC daily

GH

Liver

IGF-1

Somatic and metabolic effects: acromegaly

GHR = growth hormone receptor antagonist; IM = intramuscular; SC = subcutaneous.

Diagnosis

A biochemical evaluation should be undertaken to confirm suspected acromegaly. Since GH levels are pulsatile, random measurements are rarely useful. An oral glucose tolerance test (OGTT), utilising the normal ability of glucose to suppress GH, is the gold-standard laboratory test to confirm or exclude this disease. Failure to suppress GH levels to <1ng/ml after OGTT suggests the diagnosis of acromegaly. Since IGF-1 is an integrated marker of GH secretion, an elevated IGF-1 level compared with an age- and gender-normative data range is supportive of the diagnosis. Following biochemical diagnosis, a magnetic resonance imaging (MRI) scan should be performed to determine the presence of a pituitary adenoma and to assess for local mass effects. If a macroadenoma is present, it is important to evaluate for hypopituitarism, especially adrenal insufficiency (which needs to be rapidly treated), and to assess for visual field compromise.

Treatment

Goals of Therapy

The specific goals of treatment are to:

- normalise disease markers (GH and IGF-1);
- slow or reverse the clinical signs and symptoms;
- preserve normal pituitary function; and
- restore life expectancy to that of the general population.

Although controversial, most experts agree that disease control is defined by normal serum IGF-1 levels and attainment of a safe GH level, such as mean basal serum GH <2.5ng/ml or a GH level following an OGTT of <1ng/ml.[10,11] There are three major treatment modalities to achieve these end-points: surgery, medical therapy and radiation, which are described in detail below.

Surgery

Trans-sphenoidal surgery is the primary modality of therapy in the majority of cases because it can yield a rapid cure and correct local mass effects. Transfrontal craniotomy is uncommonly utilised as the surgical

approach for more aggressive, invasive tumours. The cure rate for a well circumscribed intrasellar microadenoma (<1cm) is approximately 90%.[12] In contrast, surgical efficacy rates for macroadenomas are lower and range from 30 to 70%. In subjects in biochemical remission following surgery, long-term relapse rates have been reported in up to 19% of subjects, potentially due to dural remnants.[13] Cure rates depend on tumour size and location (with lower efficacy rates in the presence of extrasellar involvement, including cavernous sinus invasion), pre-surgical GH levels and surgical expertise.[14,15]

Complications of surgery are infrequent but include visual impairment, meningitis or cerebrospinal fluid leak, anterior or posterior pituitary hormone dysfunction and local nasal complications. Following surgery, subjects should undergo repeat biochemical testing with serum IGF-1 and basal GH levels at approximately eight to 12 weeks to determine surgical efficacy. Since most patients with acromegaly have a macroadenoma at the time of presentation, many do not attain a surgical cure, and in these cases additional therapeutic options may be necessary. Re-operation is considered for residual disease, but is usually ineffective in the presence of extra-sellar tumour invasion. Therefore, further adjuvant therapy is recommended for such patients.

Medical Therapy

Medical therapy is usually considered in an adjuvant role for patients with residual disease following surgery. There are three classes of medical options: somatostatin analogues (SAs), dopamine agonists (DAs) and a GH receptor (GHR) antagonist (see *Figure 1*).

Somatostatin Analogues

SAs (octreotide and lanreotide) bind to somatostatin receptor (SSTR) subtypes 2 and 5 on somatotroph adenomas to suppress GH release. Both octreotide (octreotide LAR) and lanreotide (lanreotide autogel) are most commonly administered as long-acting-release preparations at monthly intramuscular injections. SAs result in GH control and normalisation of serum IGF-1 levels in approximately 50–70% of cases, although this number may be exaggerated as many studies pre-select subjects for SA-responsive tumours.[16] Biochemical response reflects expression of the SSTR2 expression and tumour size.[17] As an adjuvant therapy, octreotide LAR administration leads to modest tumour shrinkage by 10–50% in 47% of subjects.[16] Side effects of SAs include gastrointestinal (GI) upset (which usually improves over time), gallstones in up to 40%, hair loss and bradycardia. Hyperglycaemia may occur, although insulin sensitivity and high-density lipoprotein (HDL) levels may improve with prolonged SA therapy.[18,19]

Dopamine Agonists

Although DAs reduce GH levels, there is a limited therapeutic role for this option in the management of acromegaly. Bromocriptine normalises IGF-1 values in fewer than 10% of cases.[20] In contrast, cabergoline (a non-ergot, D2-receptor-specific DA) has been reported to normalise IGF-1 levels in up to 39% of cases.[21] In this study, improved biochemical response was detected in subjects with mild biochemical disease activity and/or hyperprolactinaemia. These data suggest that cabergoline may be more effective than bromocriptine. Other studies have not confirmed the prognostic value of prolactin co-production by a GH-secreting adenoma in predicting successful DA response.[22] Some advantages of DAs include the availability of oral formulations and the relatively low cost compared with other modalities. In summary, DAs may be considered as an

adjuvant medical option, primarily in subjects with limited symptoms and modest biochemical disease. It has also been suggested that the addition of DAs to SAs may have additive effects, and may be considered in patients with limited SA responsiveness.[22] Cabergoline administration has been reported in patients with Parkinson's disease (PD) to be associated with the presence of valvular heart disease (VHD), although the association was seen with doses higher than those used in the routine management of pituitary disorders. The implication of this finding for the management of subjects with acromegaly is unclear.

Growth Hormone Receptor Antagonist

The GHR antagonist pegvisomant is an engineered human GH molecule with enhanced binding to the GHR and results in functional blockade of GH-mediated intracellular signaling. This results in a reduction in circulating serum IGF-1 that is long-lasting and is associated with improvement in soft-tissue enlargement and quality of life.[23,24]

In a randomised, double-blind, placebo-controlled 12-week study, pegvisomant administration resulted in a dose-responsive reduction in IGF-1, with normalisation of IGF-1 levels in 89% of subjects.[24] Serum GH levels can increase in response to pegvisomant, and therefore should not be measured as a disease marker in subjects receiving this medication. There is concern that the increase in GH levels may reflect growth of the pituitary tumour, and there have been rare reports of tumour growth. This issue was addressed further in the German Pegvisomant Observational Study, which followed 229 patients on pegvisomant for a mean duration of 51.8±35.8 weeks.[25] In this study, tumour growth was initially detected in 12 patients (5.2%). Percentage change in size of tumour was not reported in this study; however, only four cases (1.7%) were found to have significant tumour growth. Longer follow-up is necessary to determine the clinical ramifications of this finding, though serial MRI scanning should continue to be performed. With regard to the risk of liver dysfunction, the same study reported elevated liver enzymes (>3x normal) in 12 patients (5.2%) on long-term pegvisomant therapy. In seven of these subjects, transaminases spontaneously normalised during continued treatment. In four cases, transaminase levels normalised after treatment discontinuation, and in one patient levels decreased but remained elevated during continued drug treatment.[25] Liver function should therefore be monitored in serial fashion. Pegvisomant administration has favourable effects on glucose homeostasis, including a reduction in insulin and glucose levels, and therefore may be particularly useful in the setting of acromegaly associated with type 2 diabetes mellitus.[26]

Combined use of pegvisomant and a somatostatin analogue has been shown to be effective, and combination therapy may be associated with less frequent pegvisomant dosing frequency and, potentially, reduced overall cost.[27,28]

Primary Medical Therapy – Evolving Therapeutic Paradigms

Primary medical therapy for acromegaly, either as pre-operative therapy to improve surgical outcome or as *de novo* therapy, has been suggested as an alternative to traditional paradigms. Although there are reports of improved surgical outcome following SA therapy prior to surgery, there are no controlled studies that demonstrate this. Therefore, SAs are recommended pre-operatively only to improve significant co-morbidities or when surgery is delayed. For example,

Figure 2: Mean Serum Growth Hormone Responses to Octreotide Administration
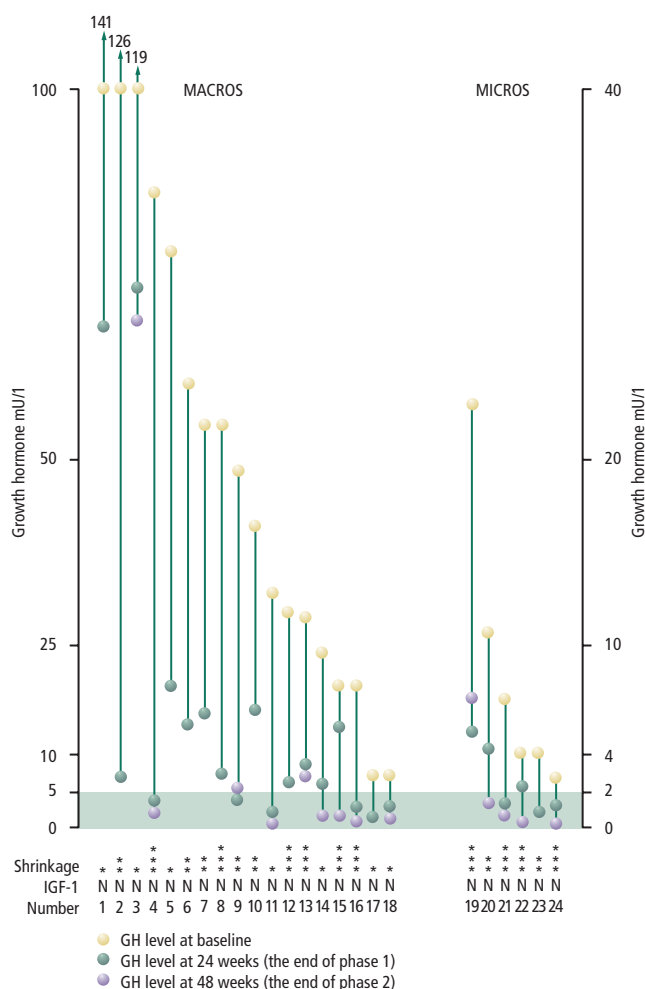
Mean serum GH responses to octreotide administration in 18 patients with GH-secreting macroadenomas (left panel) and six patients with GH-secreting microadenomas (right panel). The shading indicates controlled GH levels.
Asterisks indicate the amount of tumour shrinkage at latest assessment
(* <30%; ** 30–60%, *** >60% tumour volume reduction).
N = normal age-related IGF-I. Used with permission from Bevan et al.[14]

pre-operative SA therapy can be offered to patients with co-morbidities that increase the anaesthetic risk, such as retropharyngeal thickness (which may complicate intubation), severe hypertension and uncontrolled diabetes.

There has been much interest in the utility of SAs as *de novo* acromegaly therapy, especially in treating macroadenomas without associated localised mass effects, such as visual field loss. This option is supported by several studies showing that SAs have similar efficacy in controlling biochemical secretion, whether used in a primary or an adjuvant role.[29]

In 24 subjects naïve to any therapy, Bevan et al. showed that daily subcutaneous octreotide followed by monthly octreotide depot injections for up to 48 weeks normalised IGF-1 in 53% and GH in 79% of patients (see *Figure 2*).[30] Similar studies have demonstrated that *de novo* SA therapy results in tumour shrinkage to a greater degree and in a greater percentage of subjects than noted with adjunctive use.[31] In two recent prospective studies of patients with acromegaly (72–82% due to macroadenomas), octreotide LAR normalised IGF-1 levels in 34–70.1% of

patients and significantly reduced tumour volume (by >20%) in 75–82% of patients.[32,33] Mercado et al. reported that smaller tumour volume (microadenoma) and lower basal GH values were more predictive of improved response.[32] Although there are no controlled studies to date showing that SA therapy is equivalent or superior to surgery in a primary treatment role, there are sufficient data to suggest that primary medical therapy may be offered safely and with benefit to selected patients who are poor candidates for surgical cure. Recent consensus guidelines suggest that medical therapy may be considered in lieu of surgery for tumours not causing local mass effects, and this decision should include discussion of cost, operative risk and patient preference.[11]

Radiation Therapy

Radiation therapy is considered as an adjuvant option for patients who have failed surgery and/or are unresponsive to, or are poorly tolerant of, medical therapy. Post-operative conventional fractionated radiotherapy controls the disease in 5–78% of subjects, but it may take many years for the effects to be seen.[34,35]

Additional concerns of radiation include the risk of hypopituitarism, damage to optic structures, cerebrovascular disease and the rare occurrence of secondary tumours. Stereotactic radiosurgery (SRS) is able to deliver radiation more precisely than conventional radiation. Some studies suggest that SRS may control disease sooner than with conventional radiation.[36] For example, in a prospective study of 82 subjects with active acromegaly, 63 of whom had previous trans-sphenoidal surgery, gamma knife SRS resulted in remission in 17% of subjects at a mean follow-up of 49.5 months. An additional 23% of subjects, previously uncontrolled by SAs, achieved disease control with SAs after gamma knife radiosurgery.[37]

More recently, Jezkova et al. reported that 50% of 96 subjects treated with gamma knife radiosurgery had normalisation of serum IGF-1 within 54 months.[38] The incidence of hypopituitarism secondary to SRS appears to be similar to that of conventional radiotherapy in studies published to date. Further studies are important to determine the overall role of SRS in the management of acromegaly.

Conclusion

Acromegaly is a disease characterised by GH hypersecretion, and is associated with multiple medical co-morbidities and premature mortality. With successful treatment, life expectancy in acromegaly may be restored to normal. There are several effective treatment modalities available, with evolving paradigms in their use. With recent advances in the management of acromegaly, disease control can be reasonably expected in the majority of patients. ■

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