Are We Achieving Pharmacological Disease Control in Acromegaly?

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Abstract

Acromegaly is a rare endocrine disorder, associated with significant morbidity and mortality due to the harmful effects of prolonged exposure to increased levels of growth hormone (GH) and its effector, insulin-like growth factor-1 (IGF-1). The most common cause of acromegaly is a pituitary adenoma, for which surgical resection is usually the first choice treatment. In cases where surgical resection is not possible, or where the patient declines surgery, somatostatin analogues (SSAs) are used as first-line medical therapy. Other therapeutic options include dopamine antagonists and the GH receptor antagonist – pegvisomant. In addition, considerable current research is investigating the clinical utility of combined therapies. Disease control is defined in terms of reduction of GH and IGF-1 normalisation and reduction in mortality levels to those seen in the general population. Reported disease control rates of acromegaly are highly variable and it has been reported that treatment efficacy in clinical practice is considerably lower than the success rates reported by reference centres. There is therefore a substantial need for improved disease management strategies for acromegaly.

Keywords

Acromegaly, growth hormone, insulin-like growth factor, pegvisomant, somatostatin analogue

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Acromegaly is an endocrine disorder and is characterised by soft tissue enlargement and excessive skeletal growth with acral enlargement and coarse facial features. The incidence of acromegaly is approximately 3.3/1,000,000.0/year and the prevalence is 60/1,000,000.[1] Although a rare condition, the clinical, economic and health-related quality of life (HRQoL) burden associated with acromegaly is considerable owing to its broad spectrum of co-morbidities as well as the need for lifelong management. Acromegaly is diagnosed in approximately equal numbers of men and women, and the mean age at diagnosis for both sexes is in the early to mid-40s.[2]

The features of acromegaly develop slowly over decades, and diagnosis can be delayed up to 10 years after the onset of symptoms.[3] Excessive levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) cause major structural and functional cardiac changes, and as a result the disease has numerous clinical manifestations ranging from acral overgrowth to myocardial hypertrophy and diastolic heart failure (see *Table 1*).[4] One study found that the most common presenting symptoms are acral enlargement (in 86 % of patients), maxillofacial change (74 %), excessive perspiration (48 %), arthralgia (46 %), headache (40 %) and hypogonadal symptoms (38 %).[5] In young patients acromegaly occurring before the closure of epiphyseal bone results in accelerated growth and gigantism. However, this is very rare, in a review of 2,367 children and adolescents with pituitary adenomas, only 0.6 % had gigantism.[6]

Acromegaly is also associated with a high incidence of co-morbidities: one study (n=100) reported multiple co-morbidities in 40 % of patients.[7] GH excess in acromegaly negatively impacts glucose homeostasis, and is associated with hypertension, which are believed to be major contributors to the increased cardiovascular risk associated with the disease.[8] Acromegaly is associated with several abnormalities of the cardiovascular system and control of GH/IGF-1 secretion can reverse cardiovascular abnormalities.[9] An increased arterial intima-media thickness of both the carotid arteries has been observed in patients with acromegaly. However, the prevalence of well defined carotid plaques was not increased in both groups of patients with acromegaly as compared with controls, suggesting that cardiovascular risk resulting from GH and IGF-1 excess in acromegaly is associated with heart rather than vascular abnormalities.[10] Further co-morbidities include lipid abnormalities, arthritis, hypertension and sleep apnoea.[11]

Although advances in the management of acromegaly have led to an increased number of patients achieving biochemical control over the long-term, elevated levels of GH and IGF-1 in acromegaly are associated with a twofold increase in mortality levels to those similar to the general population.[12,13] Causes of mortality are similar to those of the general population but with an excess of death from cardiovascular disease.[14] The most frequent cause of death in acromegaly is cardiomyopathy, the prevalence of which is 3.3–14.2 times higher in the acromegalic versus the non-acromegalic population.[15]

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Table 1: Clinical Features of Acromegaly

Symptom	
Direct Effects of the Tumour	
	Headache
	Visual field defects
	Hyperprolactinaemia
	Cranial nerve palsy
	Hypopituitarism
	Hypothyroidism, hypogonadism, hypocortisolism
Systemic Effects of Growth Hormone/Insulin-like Growth Factor-1 Excess	
Soft tissue and skin changes	Visceromegaly
	Acral enlargement, including thickening of tissues of hands and feet
	Increased skin thickness and soft tissue hypertrophy
	Hyperhidrosis
	Colon polyps
	Skin tags and acanthosis nigricans
Cardiovascular system	Hypertrophy (biventricular or asymmetric septal)
	Congestive heart failure (systolic and/or diastolic)
	Coronary disease
	Arrhythmias
	Hypertension
	Cardiomyopathy
Metabolic features	Impaired glucose tolerance
	Diabetes
	Insulin resistance
Respiratory symptoms	Macroglossia
	Jaw malocclusion
	Upper airway obstruction
	Sleep disturbances
	Sleep apnoea
	Ventilatory dysfunction
Bone and joint manifestations	Increased articular cartilage thickness
	Arthralgia and arthritis
	Carpal tunnel syndrome
	Osteopenia
Other endocrine symptoms	Goitre
	Hypercalciuria
	Galactorrhoea
	Hyperparathyroidism

Source: Based on information from Colao et al., 2004,[8] Feelders et al., 2009[25] and Melmed, 2006.[4]

More than 90 % of cases of acromegaly are caused by a benign GH-secreting adenoma in pituitary somatotroph cells.[16] The increases in morbidity and mortality associated with acromegaly result not only from oversecretion of GH and IGF-1 but also from the effect of the tumour mass. GH induces the synthesis of peripheral IGF-1 which induces cell proliferation and inhibits apoptosis.[17] Somatostatin regulates the release of GH, and its biological action is mediated by five somatostatin receptors (SSTRs). Approximately 90 % of GH-secreting pituitary adenomas express SSTR subtypes 2 and 5 (SSTR2 and SSTR5).[4] In the presence of somatostatin, these receptors signal the pituitary gland to suppress GH secretion.

Advances in understanding the cellular origin of pituitary tumours have led to significant improvements in approaches to the treatment of acromegaly, and tight biochemical control of the disease can reduce mortality levels to compare with those of the general population.[13] The aim of this article is to discuss the criteria for disease control, review studies detailing the efficacy of various therapeutic strategies in management of the disease and to highlight the fact that currently used pharmacological therapies may not be achieving adequate disease control.

Table 2: Percentage of Patients Treated by Radiotherapy, Surgery, or by Primary Medical Treatment According to Year of Diagnosis

Year	Percentage of Patients by Treatment Type		
	Radiotherapy	Surgery	Primary Medical
<1980	69	48	12
1980–1989	49	84	10
1990–1994	34	78	21
1995–1999	30	68	31
>2000	8	61	39

Source: Bex et al., 2007.[30]

Diagnosis

The onset of the symptoms in acromegaly is insidious and most signs are insufficiently characteristic to allow early diagnosis. However, early detection of the disease is crucial to prevent the development of irreversible complications, including cardiomyopathy, respiratory dysfunction and arthropathy.[8] Patients with an estimated disease duration of >10 years have a relative risk of cardiac complications three-times higher than patients with estimated disease duration ≤5 years.[18] Growth of acral parts, which may be observed as an increase in shoe or ring size, is often the reason for patients to seek medical advice. Diagnosis may begin with a clinical suspicion from a physician who is working in a field other than endocrinology. For example, a dentist may recognise a bite malocclusion typical of a patient with acromegaly whose lower jaw is protruding further than the upper jaw, or an ophthalmologist may find a visual field defect.

Biochemical analysis is usually necessary to confirm a diagnosis of acromegaly. Diagnosis is based on the finding of elevated IGF-1 levels, and a failure to suppress GH in response to an oral glucose tolerance test (OGTT). Unlike the general population, acromegaly patients do not suppress GH secretion in response to glucose. A post-OGTT GH level >0.4 µg/l is the most recently designated cut-off level used to diagnose acromegaly.[19] Serum prolactin should also be measured in all patients diagnosed as having acromegaly because prolactin cosecretion can identify a subset of patients at elevated risk of disease persistence after surgery.[20] Acromegaly causes typical changes of the face in the early stages of the disease, and recent research has suggested that face classification software may be able to identify subtle facial features indicative of the disease that are difficult to visually identify and may thus be a useful diagnostic tool.[21]

Measuring Disease Control in Acromegaly

The treatment goals for patients with acromegaly include:

- normalised IGF-1 levels;
- reduction of GH levels to <1 µg/l;
- removal or control of tumour mass;
- relief of signs and symptoms of the disease; and
- reduced mortality rates to those seen in the general population.

Treatment of acromegaly can also result in significant improvements in co-morbidities such as cardiovascular disease.[22] A consensus guideline on the criteria for the cure of acromegaly was published in 2010, and disease control is defined as:

- a random or mean GH level of <1 µg/l;
- a nadir GH level after OGTT of <0.4 µg/l; and
- achievement of age and sex normalised levels of IGF-1.[19]

Table 3: Pharmacological Therapy of Acromegaly

Drug Type	Indications	Dosage	Biochemical Control*	Effect on Tumour	Adverse Effects
SSAs	1st line where surgery contraindicated, post-op where poor biochem control, prior to radiotherapy	OCT-SR 100 µg/day, OCT-LAR 20 mg IM every 4 weeks, LAN-SR 30 mg IM every 7–14 days	Reports of efficacy range from 7.1–70.0 %, depending on whether used as 1st or 2nd therapy, and whether patients were preselected for their response to SSAs	50 % mass reduction	Biliary tract disease, impaired glucose tolerance, GI symptoms
DAs	Where oral medication preferred, cost factors, elevated prolactin, combination with SSAs	CAB 1–4 mg weekly	<15 %	none	GI symptoms, postural dizziness, nasal congestion, valvular heart complaints
GH receptor antagonists	High IGF-1 despite other treatment, combination with SSAs	PEG 40 mg SC loading dose, then 10 mg daily	>90 % IGF-1 normalisation, ↑ GH	none	↑ liver function test, injection site lipohypertrophy, hypercholesterolaemia

**Growth hormone (GH) < 2.5 mg/l or normalisation of insulin-like growth factor-1 (IGF-1). CAB = cabergoline; DAs = dopamine agonists; GI = gastrointestinal; IM = intramuscular; LAN-SR = lanreotide slow release; OCT-LAR = octreotide long-acting repeatable; OCT-SR = octreotide slow release; PEG = pegvisomant; SC = subcutaneous; SSAs = somatostatin analogues. Sources: Colao et al., 2006[21] and Manjila et al., 2010.[16]*

A study found that overall IGF-1 levels (especially discordant levels) are more predictive than GH in terms of insulin sensitivity, a common metabolic abnormality in active acromegaly, and clinical symptom score.[23] While elevations in GH generally correlate to elevations in IGF-1, discordance (elevated IGF-1 and normal GH, or elevated GH and normal IGF-1) has been reported in 9–39 % of patients receiving medical therapy for acromegaly, complicating treatment decisions. Management of patients with discordant levels of IGF-1 and GH requires expertise and should be individualised.[24]

Reported disease control rates of acromegaly are highly variable,[25] and this may be a result of differences between these studies in the criteria used to determine these rates that include:

- study design (prospective versus retrospective studies);
- patient population (selected or non-selected patients for response);
- expert centres involved; and
- the type of assays used to determine biochemical control.[19]

In the course of the past decade, techniques used for measuring GH and IGF-1 have changed and immunoassays for GH have become considerably more sensitive. However, there is a lack of validation and standardisation data relating to the new assays, and a lack of uniformity in reference standards.[26] In addition, there can be daily fluctuations in GH levels, and normal levels are age and sex dependent. IGF-1 levels can also be influenced by age, gender, season, nutritional status and co-morbidities.[26] A recent consensus statement concluded that considerable improvements are required in the areas of GH and IGF-1 assay performance and comparability, and it recommended that a commutable standard for each assay be implemented for worldwide use.[27]

A recent review suggested that the response to somatostatin analogues (SSAs) in acromegaly should be assessed by considering the biochemical effects and those on tumour mass because only the lack of both responses is indicative of a poor response or resistance. The latter evidence occurs in less than 25 % of SSA-treated patients after 12 months.[28]

Treatment of Acromegaly

Current treatment options for acromegaly include neurosurgery, radiotherapy and medical treatment. However, complete surgical excision of the underlying pituitary adenoma is not achieved in a significant proportion of patients, because it is important not to damage surrounding healthy tissue, and further treatment is often needed after surgery to reduce GH levels. A multimodal approach is usually employed, with surgery as the first-line of treatment, followed by medical therapy for residual disease. Radiation treatment is usually reserved for refractory cases. Radiation can achieve durable tumour control but its disadvantages include a lag time of several years to response owing to its slow lowering of GH and IGF-1 levels, the development of hypopituitarism in over 50 % of patients, and the risk of cerebrovascular events (21 % at 20 years) and secondary brain tumours (2 % at 20 years).[11] Stereotactic radiotherapy (SRS) is a more precise technique of irradiation with biochemical remission reported in 30–60 % of patients following treatment with this technique.[29]

Surgery is considered the most effective option to achieve rapid and complete cure and remains the most common first-line treatment, particularly in patients with enclosed adenomas, although the proportion of patients receiving primary medical therapy has risen in recent years (see *Table 2*).[30] Even if complete surgical resection cannot be achieved, the reduction in tumour mass resulting from debulking surgery can lead to a considerable reduction of symptoms and increases the likelihood of achieving biochemical disease control.[31] Most surgical procedures employ minimally invasive, endoscopic transsphenoidal techniques which can achieve biochemical response in approximately 40–60 % of patients.[25,32]

Medical therapy is indicated in patients who fail to achieve remission after surgery, in rare patients for whom surgery is contraindicated or in patients who are unlikely to achieve biochemical control with surgery. It is also used following radiotherapy.[33] There are three classes of medical therapy: dopamine agonists (DAs), SSAs and a GH receptor antagonist – pegvisomant (see *Table 3*). All have shown varying degrees of efficacy in clinical trials (see *Table 4*).

DAs such as cabergoline are sometimes preferred by patients and physicians because they are inexpensive and administered orally. However, they are effective only in a minority of patients – DA agonists alone showed a 13 % disease control rate in a Belgian registry study.[30] A recent meta-analysis (15 studies, 227 patients) found that cabergoline monotherapy normalises IGF-1 levels in one-third of patients with acromegaly, though none of these studies were randomised or placebo-controlled.[34]

Table 4: Summary of Studies Examining the Efficacy of Pharmacological Treatments in Acromegaly

Drug	Number of Patients	Study Design	Study Details	Results	Limitations of Study	Reference
OCT (SC)	189 (unselected patients with active acromegaly)	Multicentre, prospective	Treated six d-231 week; SC OCT 100–1,500 µg/d;13 on SC infusions; dose escalation based on clinical and biochemical response	Mean GH decreased in 94 %; IGF-1 decreased in 92 %; GH <5 µg/l in 45 %; IGF-1 in 46 %. Tumour size decreased >20 % in 44 %	GI or local injection site side effects in 37 %; Glucose tolerance reduced in 48 %	62
OCT (SC)	115 (unselected patients with active acromegaly)	Double blind, randomised	Initial four week randomised to SC OCT tid or placebo; four week WO, then randomised to 6 months SC OCT 100 or 250 mg tid	In first phase 26 % with GH <5 µg/l achieved GH <2 µg/l, and 58 % with raised IGF-1 normalised on OCT. In 6 month treatment, 21 and 16 % on 250 and 100 mg tid achieved GH <2 µg/l, 68 and 55 % normalised IGF-1 levels, 19 and 37 % on high and low dose showed tumour size reduction (>1 mm diameter)	Dose fixed and not titrated to optimise biochemical response; Non age-related reference range for IGF-1	63
LAN-SR	118 (unselected patients with active acromegaly)	Multicentre, open label, prospective	SC OCT titrated to max dose of 600 µg/d, WO 4–8 week, then LAN-SR 30 mg 2 weekly for 3 months. Dose frequency increased to every 10 d if GH >2.5 µg/l after 3 month LAN-SR. Duration 24 months	SC OCT resulted in GH <2.5 µg/l and normalised IGF-1 in 34 and 7 % of patients, respectively. At 24-months LAN-SR, GH and IGF-1 levels controlled in 77 and 63 %, respectively. Significant tumour shrinkage (>20 % volume)	Open design; SC OCT dose limited to 600 µg/d; LAN-SR dose titrated up to a max of 30 mg every 10 days	64
LAN-SR	66 (unselected patients with active acromegaly)	Multicentre, open label, prospective	LAN-SR 30 mg every 14 days. Dose frequency increased to every 10 days if IGF-1 not controlled at 3 months, and to every 7 days if IGF-1 elevated at 6 months; 55 patients previously treated with SC OCT for mean 31.7 months	In patients previously treated with SC OCT, 35 % achieved a normal IGF-1 level. After 12 months LAN-SR, 45 and 44 % achieved GH <2.5 µg/l and normal IGF-1. Tumour shrinkage >25 % volume in 36 % at 12 months	Open design. Prior treatment with SC OCT not in a study setting and may not have been optimised	65
OCT-LAR	151 (preselected patients showing a positive response to octreotide)	Multicentre, open label, prospective	European multicentre study. Individualised SC OCT for 4 weeks until GH <10 µg/l. Thereafter OCT-LAR 20 mg 4 weekly for 3 months. At 3 months if GH <1 µg/l, dose reduced to 10 mg, and if GH <5 µg/l, dose increased to 30 mg 4 weekly. Study duration 48 weeks	GH <2.5 µg/l in 65.8 % on SC OCT and 70 % on OCT-LAR. IGF-1 values were normal in 63 % on SC OCT and 66 % on OCT-LAR	Open design. Patients selected on basis of known responsiveness to OCT. Unclear if SC OCT optimised	66
OCT-LAR	110 (preselected patients showing a positive response to octreotide)	Retrospective	OCT-LAR initiated at 20 mg 4 weekly and dose adjusted to achieve GH <2.5 µg/l and normalised IGF-1. Mean duration of follow-up 30 months	At study completion 72 and 75 % achieved GH <2.5 µg/l and normal IGF-1, respectively. Tumour volume reduction >25 % in 46 % patients, and 77 % of primary therapy group	Open design. Only patients with a 20 % or greater decrease in GH and/or IGF-1 after 6 months continued in the study	67
CAB	64 (unselected patients with active acromegaly)	Multicentre, prospective, open label	Dosage 1.0 mg/week gradually increased until normalisation of IGF-1 or max weekly dose of 3.5 mg	Suppressed plasma IGF-1 <300 µg/l in 39 % and between 300–450 µg/l in another 28 %	Open design. Some patients had prior surgery and/or radio-therapy and moderate elevations of IGF-1. Some had initial GH levels below 5 µg/l	68
PEG	112 (unselected patients with active acromegaly and no LAR somatostatin use in the last 12 weeks)	Randomised, double blind	12 week study of 3 daily doses of PEG (10 mg, 15 mg, and 20 mg) and placebo, given subcutaneously	Mean IGF-1 normalised in 10 % of placebo group, 54 % with 10 mg PEG/d, 81 % with 15 mg PEG/d, 89 % with 20 mg PEG/d ($p<0.001$). With 15 mg/20 mg PEG/d, significant decreases in ring size, soft-tissue swelling, excessive perspiration, and fatigue. Score for total symptoms and signs of acromegaly decreased significantly in all groups receiving PEG ($p\leq0.05$)	Short duration	69

CAB = cabergoline; GH = growth hormone; GI = gastrointestinal; IGF-1 = insulin-like growth factor-1; LAN-SR = lanreotide slow release; LAR = long-acting repeatable; OCT = octreotide; PEG = pegvisomant; SC = subcutaneous; tid = three times daily; WO = washout.
Source: Adapted from Murray and Melmed et al., 2008.[37]

SSAs are the most widely used medical treatments for acromegaly and can achieve disease control after one month of treatment (see *Figure 1*).[35] The rationale behind their use is based on the inhibitory effects of native somatostatin on GH secretion. Initial formulations of the SSA octreotide were administered by subcutaneous (SC) injections three times a day. A 1997 study showed that pre-treatment

for 3–6 months with octreotide before surgery improved clinical conditions and surgical outcome.[36]

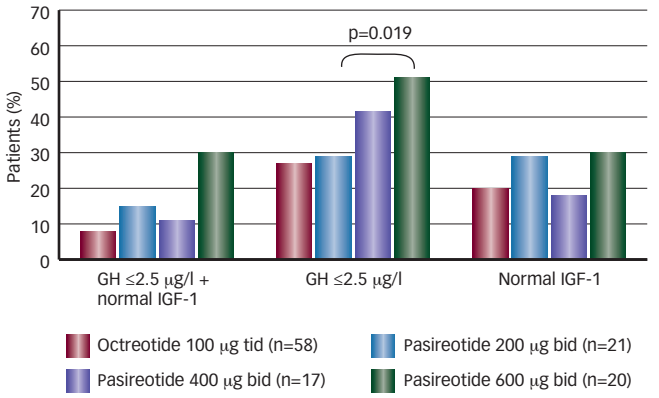
More recent formulations of SSAs are longer acting and necessitate intramuscular or deep SC injections usually every four weeks, although a minority of patients can be treated every six weeks or longer. Two slow release formulations are available: octreotide long-acting repeatable (OCT-LAR) and lanreotide Autogel®.[33] A critical analysis found that all formulations had equivalent efficacy.[37] Predictors of response include gender, age, initial GH and IGF-1 levels, tumour mass and adequate expression of SSRT2 and SSRT5.[28] Treatment with OCT-LAR for 12 months has been found to reverse acromegalic cardiomyopathy in most young patients (age <40 years) with short disease duration and achieving disease control.[38] In another study, the majority of patients with acromegaly (75.5 %) had 25 % or greater tumour shrinkage after 12 months of primary treatment with SSAs.[39]

Recent data suggest that first-line treatment with SSAs has equivalent efficacy to surgery,[40] and that SSAs are associated with improved cardiac outcomes.[41] Evidence indicates that pre-operative treatment with lanreotide or OCT-LAR results in a better post-operative outcome.[42,43] SSAs have also demonstrated impressive long-term efficacy and safety as first-line therapy: SSA therapy for five years controlled GH in 100 % of cases and IGF-1 in 97.8 %, as well as resulting in tumour shrinkage by a median 80 %, and significant improvements in hypertension, cardiac performance and dyslipidemia.[41]

The GH receptor antagonist pegvisomant has high efficacy but is the most expensive of the currently available medical therapies. A 52-week, multicentre, open-label, randomised study (n=118) concluded that pegvisomant and OCT-LAR were equally effective at normalising IGF-1 in the overall population, and pegvisomant was more effective in patients with higher baseline IGF-1 levels. Pegvisomant had a more favourable effect on parameters of glycaemic control.[44] In patients treated with pegvisomant for a year, IGF-1 levels were normalised in 97 % of patients following adequate dose titration.[45] Patients also reported improvements in signs and symptoms of acromegaly. A recent global safety surveillance study (n=1,288) of long-term treatment of acromegaly with pegvisomant concluded after five years of treatment, 63.2 % of subjects had normal IGF-1 levels at a mean dose of 18 mg/day.[46] The treatment was generally safe and well-tolerated. To be cost-effective, however, a UK study suggested that the price of pegvisomant should be reduced by one-third.[47]

Cost savings may be achieved by the use of combination therapy, enabling lower drug doses. Several studies have demonstrated the efficacy of combination therapy in acromegaly. In a study of 10 patients with acromegaly who were poor responders to octreotide, treatment with the combination of lanreotide and cabergoline resulted in suppression of serum GH and normalisation of plasma IGF-1 levels in 40 and 50 % of patients, respectively, after three months.[48] In a recent study, co-administration of lanreotide Autogel and pegvisomant normalised IGF-1 levels in 57.8 % patients with acromegaly partially controlled by SSAs alone.[49] In one study the combination of monthly SSAs and weekly pegvisomant resulted in normalisation of levels in 18 of 19 (95 %) patients who completed 42 weeks of treatment.[50] Another study demonstrated that this combination resulted in significant improvements to patient QoL.[51] Long-term combined treatment with SSAs and twice-weekly pegvisomant has been shown to be safe up to more than four years.[52] A recent prospective clinical study suggested

Figure 1: Percentage of Patients who Achieved a Growth Hormone (GH), Insulin-like Growth Factor-1 (IGF-1) or GH Plus IGF-1 Response After One Month of Treatment with Octreotide or Pasireotide, by Dose



All patients received octreotide 100 µg three times daily (tid) for one month followed by one month of pasireotide 200, 400, or 600 µg twice daily (bid). Results after one month octreotide and one month octreotide plus one month pasireotide are presented here. GH = growth hormone; IGF-1 = insulin-like growth factor-1. Source: Petersenn et al., 2010.[35]

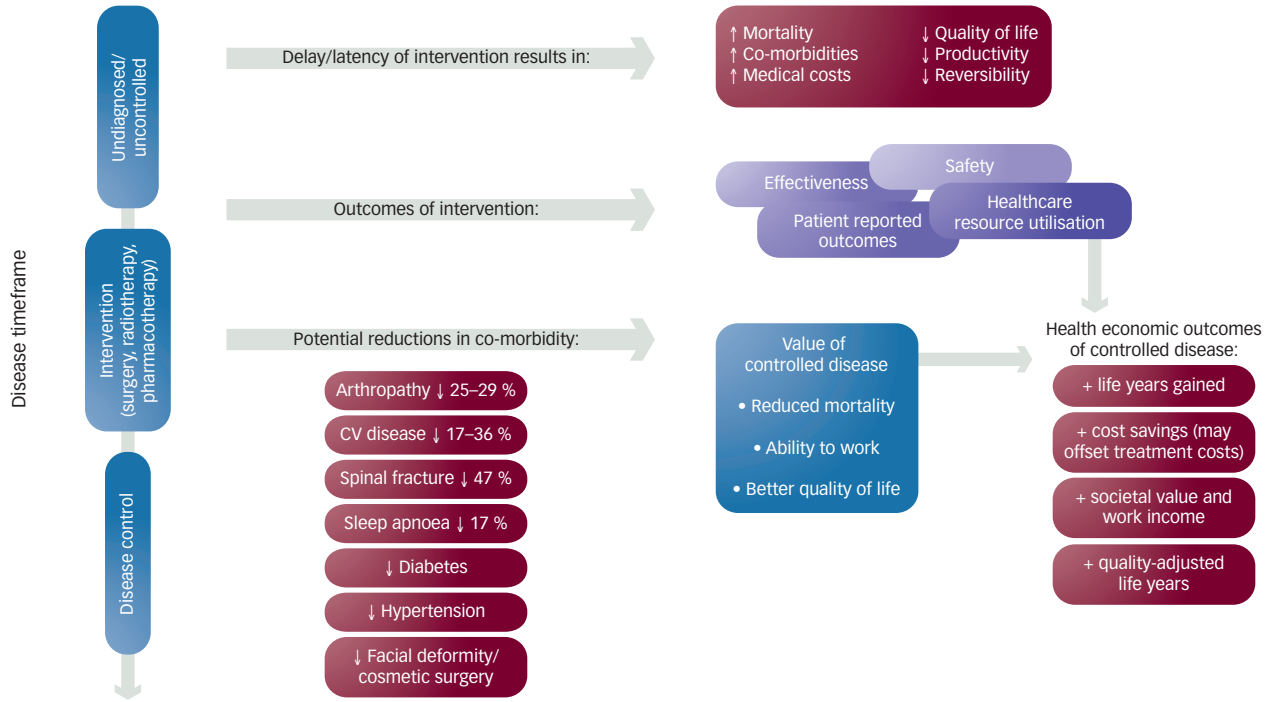
that combination treatment with cabergoline and pegvisomant is more effective at reducing IGF-1 levels than either cabergoline or pegvisomant monotherapy.[53] Additionally, pegvisomant is also useful to improve acromegaly co-morbidities.[54–57]

Acromegaly Consensus Group guidelines for the management of acromegaly suggest the use of DAs when the patient prefers oral medication or after surgery in selected patients, such as those with markedly elevated prolactin, or as additive therapy in patients with only a partial response to a maximum dose of SSAs.[17] SSAs are recommended as first-line therapy when there is a low probability of a surgical cure (for example, large extracellular tumours with no evidence of central compressive effects), after surgery has failed to achieve biochemical control and before surgery to improve severe co-morbidities that prevent or complicate immediate surgery. They are also recommended to provide partial biochemical disease control during the lag time between administration of radiation therapy and the onset of benefit. Pegvisomant is recommended in patients that have persistently elevated IGF-1 levels despite maximum doses of SSAs, and in combination with SSAs.[17]

Treatment Effectiveness in Clinical Practice

It has previously been reported that a biochemical response is achieved by approximately 70 % of patients receiving SSAs.[4] However, most of these studies have been restricted to centres of expertise, most were retrospective evaluations, and many recruited patients that were preselected for their response to SSAs, therefore not providing an accurate picture of treatment outcomes in general use. Several registry studies indicate that the effectiveness of treatment in actual clinical practice is significantly lower than those reported in clinical trials.[30,32,58] Registry studies, however, have their own limitations since they depend on the voluntary reporting of cases by all endocrinologists involved in the study, and therefore may not be complete. An epidemiological, observational, longitudinal, multicentre study of patients (n=74) with newly diagnosed acromegaly monitored disease treatment and control over two years. Surgery was the preferred initial treatment for patients with acromegaly and achieved disease control in 27 %

Figure 2: Conceptual Model of the Value of Disease Control in Acromegaly



CV = cardiovascular disease. Source: Ben-Shlomo et al., 2011.[11]

of patients. SSAs were the preferred treatment option following surgery failure and achieved disease control in more than 40 % of patients. However, of the patients receiving first-line medical treatment, only 22 % had disease control at the end of follow-up.[58]

Results from the Spanish acromegaly registry (n=1,219) showed that, of 113 patients who received first-line drug treatment to control the disease, only 7.1 % achieved disease control. Of 277 patients who received surgery and drugs, 35.7 % achieved disease control.[32] Data from the Belgian registry on acromegaly (n=418) found that primary medical therapy normalised GH and IGF-1 levels in only 24 % of acromegaly patients.[30] A retrospective analysis of the German Acromegaly Register (n=889) found that following first-line SSAs (≥3 months) GH and IGF-1 normalised in 36.3 % of patients with microadenomas and 30.5 % with macroadenomas, increasing to 40.8 and 41.5 % with longer duration of SSA treatment (≥360 days), and that surgery was more effective to lower GH and IGF-1 concentrations than primary SSAs.[59]

In summary, treatment efficacy for acromegaly in actual clinical practice is considerably lower than the success rates reported by reference centres. There is also a lack of data on the impact co-morbidities have on mortality, HRQoL and direct and indirect costs including productivity losses when the disease is not adequately controlled. Incorporation of these data into a tool, which healthcare providers and policy makers could use to evaluate treatment options and determine the most effective treatment plans, would be useful for patients. *Figure 2* presents a conceptual tool illustrating the value of disease control in acromegaly.[11]

Future Directions in the Treatment of Acromegaly

Pasireotide is a novel SSA with affinity for the receptor subtypes SSTR1, SSTR2, SSTR3 and SSTR5. Octreotide and lanreotide have the highest affinity for SSTR2, however, most GH-secreting pituitary adenomas express SSTR2 and SSTR5. A Phase II randomised, multicentre, open-label, clinical trial (n=60) found that, after 28 days of octreotide (100 µg SC three-times/day), disease control was achieved in 9 % of patients. After four weeks of pasireotide treatment disease control was seen in 19 % of patients and after three months of treatment increased to 27 %.[35] A Phase III trial comparing pasireotide LAR versus octreotide LAR with an estimated enrolment of 360 patients with acromegaly is currently ongoing (NCT00600886). Results from this study, presented at the 2012 joint 15th International Congress of Endocrinology and 14th European Congress of Endocrinology meeting (ICE/ECE) in Florence, Italy, showed that pasireotide was significantly more effective at inducing full biochemical control in patients with acromegaly than octreotide.[60]

Conclusion

Acromegaly is a challenging condition in terms of diagnosis and therapeutic monitoring. Advances in medical therapy for acromegaly, including the use of combination therapy, have expanded the role of pharmaceutical treatments in disease control. However, the role of surgery in the management of acromegaly is still important and debulking surgery may result in improved outcomes in patients with a high GH concentration and a large tumour.[59] A review of data from registry studies shows that the majority of patients with acromegaly do not achieve disease control.[30,32,58]

There remains a need for improved definition of disease control in acromegaly. Improvements in biochemical assay performance and comparability are also required, as is uniformity of reference standards. Furthermore, new therapies or combinations of therapies that provide disease control of acromegaly in the majority of patients remain an unmet clinical need. ■

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