

60 YEARS OF NEUROENDOCRINOLOGY

Acromegaly

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Abstract

Acromegaly (ACM) is a chronic, progressive disorder caused by the persistent hypersecretion of GH, in the vast majority of cases secreted by a pituitary adenoma. The consequent increase in IGF1 (a GH-induced liver protein) is responsible for most clinical features and for the systemic complications associated with increased mortality. The clinical diagnosis, based on symptoms related to GH excess or the presence of a pituitary mass, is often delayed many years because of the slow progression of the disease. Initial testing relies on measuring the serum IGF1 concentration. The oral glucose tolerance test with concomitant GH measurement is the gold-standard diagnostic test. The therapeutic options for ACM are surgery, medical treatment, and radiotherapy (RT). The outcome of surgery is very good for microadenomas (80–90% cure rate), but at least half of the macroadenomas (most frequently encountered in ACM patients) are not cured surgically. Somatostatin analogs are mainly indicated after surgical failure. Currently their routine use as primary therapy is not recommended. Dopamine agonists are useful in a minority of cases. Pegvisomant is indicated for patients refractory to surgery and other medical treatments. RT is employed sparingly, in cases of persistent disease activity despite other treatments, due to its long-term side effects. With complex, combined treatment, at least three-quarters of the cases are controlled according to current criteria. With proper control of the disease, the specific complications are partially improved and the mortality rate is close to that of the background population.

Key Words

- ▶ acromegaly
- ▶ diagnosis
- ▶ cure
- ▶ somatostatin analogs
- ▶ pegvisomant
- ▶ surgery
- ▶ radiotherapy

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Introduction

Acromegaly (ACM) is a rare, slowly progressive disease caused by a chronic excess of growth hormone (GH), and associated with significant morbidity (Colao *et al.* 2004) and increased mortality (Dekkers *et al.* 2008). Gigantism occurs when the excess of GH becomes manifest in the young, before the epiphyseal fusion.

Epidemiology

The estimated prevalence of the disease is 36–60 cases/1 000 000 population with three to four new cases

per 1 000 000 population per year (Alexander *et al.* 1980, Bengtsson *et al.* 1988, Holdaway & Rajasoorya 1999, Mestron *et al.* 2004). However, higher prevalence (86/1 000 000) has been reported in a study involving an active surveillance for pituitary adenomas (PAs; Fernandez *et al.* 2010).

The sex ratio is close to 1 and ACM is typically diagnosed in the fourth to fifth decade (Ezzat *et al.* 1994). In virtually all cases ACM is caused by a GH-secreting PA. PA are almost never malignant (Kaltsas *et al.* 2005) but are associated with significant morbidity. ACM is also

associated with a higher all-cause mortality compared to the general population (mean standardized mortality ratio (SMR) 1.72 (Dekkers *et al.* 2008)), mainly caused by cardiovascular complications (Swearingen *et al.* 1998, Mestron *et al.* 2004). Mortality rates are greater in patients treated with radiotherapy (RT; Ayuk *et al.* 2004, Mestron *et al.* 2004) and lower in those offered surgery as primary treatment (Dekkers *et al.* 2008). Reduction of GH and insulin-like growth factor 1 (IGF1) following treatment is associated with a decrease of the SMR, toward normal levels (Holdaway *et al.* 2008).

Pathogenesis

Most cases of ACM occur as a result of a sporadic GH-secreting PA. However, ACM can occur in a familial setting, either associated with other endocrine abnormalities (in multiple endocrine neoplasia syndrome type 1, McCune–Albright syndrome (Weinstein *et al.* 2001), and Carney complex (Stratakis & Horvath 1993)) or as an isolated disorder. This last condition is called familial isolated PA (FIPA); 15% of these cases harbor germline mutations of the *AIP* gene (encoding the aryl-hydrocarbon receptor interacting protein), but the responsible gene mutation is unknown in the majority of cases (Daly *et al.* 2007). GH-producing PA are the most frequent tumor type in both *AIP* mutation positive and negative FIPA cases (Cain *et al.* 2010).

Patients with apparently sporadic ACM harboring *AIP* gene mutations (3% in a cohort of 154 cases) are younger

(Cazabat *et al.* 2007) and have larger, more invasive tumors than do patients without mutations (Cazabat *et al.* 2012). Also, FIPA cases with confirmed *AIP* mutation are younger at diagnosis than both *AIP*-negative FIPA and sporadic cases (Daly *et al.* 2010, Igreja *et al.* 2010).

Genetic syndromes associated with ACM are summarized in Table 1. Specific gene mutations have been described in these cases; the prevalence of these mutations in sporadic tumors (without family history, without associated abnormalities) is much lower (1–5% harbor *menin* mutations (Agarwal *et al.* 2009) and 4% *AIP* mutations (Cazabat *et al.* 2012)).

The pathogenesis of sporadic cases is more elusive. The tumorigenesis of PA is complex and implies various abnormalities in growth factor expression and cell cycle control regulation (Boikos & Stratakis 2007a). Various mutations or alterations in the expression of cell-cycle genes, oncogenes or suppressor factors have been described. For instance, somatic activating mutations of the G-protein subunit alpha (Gs) are found in up to 40% of GH-secreting PA; these cases are more responsive to medical treatment with somatostatin (SS) analogs (SSA) (Barlier *et al.* 1998). Also, pituitary tumor-transforming gene (*PTTG*) is overexpressed in PA, including GH-secreting, and its expression may be associated with tumor invasiveness (Li *et al.* 2014).

Ectopic GH production from either ectopic PA or extrapituitary tumors (pancreas, lung, and ovary) is an exceptional occurrence (Melmed 1991). Ectopic secretion of GH-releasing hormone (GHRH) has been very rarely

Table 1 Genetic syndromes associated with acromegaly. Data from Pellegata *et al.* (2006), Boikos & Stratakis (2007b), Daly *et al.* (2007), Georgitsi *et al.* (2007) and Agarwal *et al.* (2009)

Familial syndrome	Responsible gene	Clinical characteristics	Other endocrine abnormalities	Non-endocrine abnormalities
FIPA	<i>AIP</i> in 20% Unknown in the majority of cases	Young patients (<40 years old at diagnosis) Usually macroadenomas, with extrasellar extension Less frequently controlled by surgery or SSA	None	None
MEN type 1	<i>MEN1</i> (<i>menin</i>) 11q13 in 75–80% <i>CDKN1B</i> in a minority		Pancreatic neuroendocrine tumors Parathyroid adenomas	
McCune–Albright syndrome	<i>GNAS</i> 20 q13		Precocious puberty Thyrotoxicosis Cushing's syndrome	Polyostotic fibrous bone dysplasia Café-au-lait skin pigmentation
Carney complex	<i>PRKAR1A</i> 17q22–24		Primary pigmented nodular adrenocortical disease (PPNAD) Thyroid nodules (benign/malignant)	Myxomas Skin pigmentation Gonadal tumors

reported, mainly originating from pancreatic or pulmonary neuroendocrine tumors, but also hypothalamic tumors (gangliocytoma). In such cases the pituitary gland can be enlarged and only the serum measurement of the GHRH level can lead to the positive diagnosis (Borson-Chazot *et al.* 2012).

Pathology

GH-secreting PA can be classified into two histological subtypes based on the distribution of cytoplasmic cytokeratin: densely granulated (DG) and sparsely granulated (SG). SG subtypes occur in younger patients, are larger, more invasive, and less responsive to SSA (Larkin *et al.* 2013). Various other invasiveness and/or tumor aggressiveness markers have been proposed. The MAB MIB1 labelling index and the Ki-67 nuclear antigen expression are used routinely (Jaffrain-Rea *et al.* 2002); both are higher in SG than in DG tumors and inversely correlated with the response to SSA (Kasuki *et al.* 2013, Sarkar *et al.* 2014). Other markers (e.g., vascular endothelial growth factor (Yarman *et al.* 2010) or PTTG expression (Zhang *et al.* 1999)) are mainly used in research protocols.

One-third of patients with pituitary tumors may have mixed GH and prolactin (PRL) secreting adenomas (Reddy *et al.* 2010).

Clinical features and complications

The clinical presentation of ACM patients includes symptoms and signs attributable to the hormonal hypersecretion or the pituitary mass. The typical symptoms and signs are listed in Table 2 and they lead to the positive diagnosis in 35% of cases. A similar percentage is diagnosed incidentally while examining the patient for an unrelated complaint (Alexander *et al.* 1980). Because the average time from symptoms onset to diagnosis is usually about 7–10 years (Rajasoorya *et al.* 1994), at the time of diagnosis many patients present with specific complications of the disease. The most prevalent comorbidities are arterial hypertension, sleep apnea, impaired glucose tolerance (IGT), and diabetes mellitus (DM) (Mestron *et al.* 2004).

Complications

Cardiovascular Arterial hypertension is among the most frequent complications in ACM cases, present in 36–40% of patients (Mestron *et al.* 2004, Reid *et al.* 2010). Valvulopathies and arrhythmias are also more prevalent

Table 2 Clinical manifestations of acromegaly. Data from Jadresic *et al.* (1982), Molitch (1992), Ezzat *et al.* (1994), Mestron *et al.* (2004) and Reid *et al.* (2010)

Clinical effects of hormone hypersecretion	
Skin	Thick, oily skin Hyperhidrosis – 65% Skin tags Acanthosis nigricans
Musculoskeletal system	Somatic changes (prognathism, frontal bossing, and acral enlargement) – 96–98% Arthralgias, osteoarthritis – 24% Chronic pain Hearing loss Myopathy Decreased bone quality, vertebral fractures
Cardiovascular	Arterial hypertension – 40% Cardiomyopathy Ventricular hypertrophy Arrhythmias Congestive heart failure
Metabolic	Diabetes mellitus Glucose intolerance
Gastrointestinal	Colon polyps Dental changes (separation; jaw malocclusion)
Respiratory system	Sleep apnea Upper airway obstruction Macroglossia
Visceromegaly	Goiter Macroglossia Cardiomegaly Hepatomegaly Splenomegaly
Neurological	Carpal tunnel syndrome Cerebral aneurysms Headache – 55% Decreased QoL
General	Visual (visual field defects, cranial nerves palsy) Headache – 55% Hypopituitarism

in ACM populations (Colao *et al.* 2004, Pereira *et al.* 2004). Almost a half of a small cohort of ACM patients presented complex ventricular arrhythmias (Lown III–IV) in one study, especially those with a long disease duration (Kahaly *et al.* 1992). A multicentric study performed in Italy using 24-h ECG-Holter monitoring reported a lower but still very significant rate of ventricular extrasistoles (in 33% of the ACM cases evaluated; Lombardi *et al.* 2002). Twenty-four-hour ECG-Holter monitoring might be useful in the preoperative evaluation of the patients (Fedrizzi & Czepielewski 2008), especially those with clinically detected abnormalities.

If untreated, the presence of these significant morphological and functional changes leads to a complex

cardiomyopathy characterized by concentric hypertrophy (predominantly affecting the left ventricle, found hypertrophic in 60% of cases (Colao *et al.* 2004)), diastolic dysfunction and progressive systolic impairment eventually leading to heart failure (Mosca *et al.* 2013).

Other cardiovascular risk factors are also present in ACM (elevated triglycerides, lipoprotein-a, fibrinogen, plasminogen activator inhibitor, and small dense LDL particles; Tan *et al.* 1997, Colao *et al.* 2004). Although the prevalence of coronary artery disease is not clearly increased in ACM patients and most patients belong to the low-risk category if assessed with the Framingham score (Bogazzi *et al.* 2007), aggressive management of all cardiovascular risk factors is indicated, aiming at reducing the cardiovascular morbidity and mortality (Katznelson *et al.* 2014).

Metabolic ACM is frequently associated with IGT and DM because the GH excess is associated with insulin resistance (in the liver and in periphery), hyperinsulinemia, increased gluconeogenesis, and decreased peripheral glucose uptake (Møller *et al.* 1991). DM prevalence has been variably reported (reflecting the series heterogeneity with respect to ethnicity, disease status, age, etc.), but the highest prevalence rates were 40–52% (Biering *et al.* 2000, Dreval *et al.* 2014); similarly, IGT can be found in up to 28–46% of cases (Biering *et al.* 2000, Kasayama *et al.* 2000).

The GH-lowering effect of some of the treatment methods used in ACM (surgery, pegvisomant (PEG)) improves the glucose tolerance (van der Lely *et al.* 2001, Mori *et al.* 2013), while others (SSA) have a modest deleterious effect (Mazziotti *et al.* 2009).

Respiratory Sleep apnea (manifested as snoring, disturbed night sleep with somnolence during the day) has been variably reported in from 13% (Mestron *et al.* 2004) to over 50% of cases (van Haute *et al.* 2008), more frequently in diabetic or hypertensive cases (van Haute *et al.* 2008). Most cases have obstructive sleep apnea (mediated by the GH-related soft tissue growth around the upper airways), and a minority of cases have either pure central apnea or mixed apnea (Roemmler *et al.* 2012).

Some patients have respiratory dysfunction despite elevated vital capacity (Trotman-Dickenson *et al.* 1991). Upper airway obstruction is common (due to soft tissue swelling, macroglossia) and can lead to difficult intubation at the time of surgery.

Skeletal Acromegalic arthropathy can affect up to 84% of the cases (depending on the affected joint; Miller

et al. 2008), especially older patients or females (Kropf *et al.* 2013). Carpal tunnel syndrome occurs in 20–40% of cases. Musculoskeletal pain is extremely prevalent and adversely impacts the quality of life (QoL; Miller *et al.* 2008).

GH has anabolic bone effects so bone mass is usually increased compared to normal subjects (Kaji *et al.* 2001), unless untreated hypogonadism is also present. However, a recent meta-analysis of the literature revealed a high risk of vertebral fractures in active ACM suggesting a possible low quality of the bone despite a high bone mass (Mazziotti *et al.* 2015).

Neoplastic ACM has been associated with an increased risk of certain tumors, presumably due to the stimulatory effect of the IGF1 on tumorigenesis. The best-documented data are those regarding colorectal neoplasia. The pooled odds ratio (OR) are increased for both benign tumors (2.48 for adenomas and 3.557 for hyperplastic polyps) and colon cancer (2.04–4.351) (Renehan *et al.* 2003, Rokkas *et al.* 2008). The SMR for colon cancer is also higher in active ACM (2.47) compared to the general population (Orme *et al.* 1998).

The precise mechanism for the increased risk of colon tumors is not known. Potential mechanisms include direct GH or IGF1 actions on the colonic epithelial cells, altered bile acids secretion pattern, impaired immune response mechanisms in the colon mucosa, and increased colonic length – reviewed extensively elsewhere (Renehan *et al.* 2003).

The timing of the baseline colonoscopy is still debated. Some only consider it at 50–55 years (Renehan *et al.* 2001), but even younger patients harbor colonic tumors, so initial colonoscopy at ACM diagnosis has been suggested (Terzolo *et al.* 2005). Repeated colonoscopy every 10 years in controlled ACM with a normal initial result and every 5 years in those with benign tumors or uncontrolled disease appears reasonable (Dworakowska *et al.* 2010).

The risk of thyroid nodular disease and thyroid cancer is also increased, with an OR of 6.9 and 7.5, respectively, and a prevalence of 59 and 4.3% respectively (Wolinski *et al.* 2014). Whether this reflects a specific effect of the GH/IGF1 excess or the increased worldwide availability and use of precise diagnostic techniques is controversial.

Only a circumstantial relationship between ACM and prostate or breast cancer has been described to date. Until large epidemiological studies to clarify this relationship become available, it seems prudent to offer prostate cancer surveillance to older uncontrolled male patients

and routine breast cancer prevention in females (Webb *et al.* 2002).

Other Some degree of hypopituitarism is present in up to three-quarters of the patients at diagnosis (as most GH-producing adenomas are macroadenomas; Nomikos *et al.* 2005).

As a consequence of the multiple comorbidities and the somatic changes, ACM patients have severely impaired QoL (Webb 2006), psychological impairment, increased anxiety and decreased self-esteem (Pantanetti *et al.* 2002).

Diagnosis

The biochemical diagnosis of ACM requires the confirmation of persistently elevated serum levels of GH and IGF1 (a GH-regulated protein synthesized mainly in the liver; Le Roith *et al.* 2001). In many cases the biochemical diagnosis is straightforward because the serum levels of both GH and IGF1 are markedly elevated. However, in a minority of cases, mostly with mildly active disease, the assessment can be challenging.

The random assessment of serum GH is rarely useful due to the pulsatility of normal GH secretion; however,

a random serum GH level $<0.4 \mu\text{g/l}$ together with a normal IGF1 excludes the diagnosis (Giustina *et al.* 2000).

In contrast, IGF1 serum levels are stable during the day and they have a good correlation with the GH levels (Barkan *et al.* 1988). Measuring the IGF1 in serum is the initial test indicated in all patients suspected of ACM on clinical grounds or in cases with pituitary masses; selected patients with several comorbidities commonly present in ACM can also be tested (Katznelson *et al.* 2014). Active ACM is associated with elevated IGF1 levels compared to normal subjects (Ho & Weissberger 1994), so a normal IGF1 (using age- and sex-matched reference ranges) excludes the diagnosis in most patients (Katznelson *et al.* 2014). However, certain pathological conditions (see Table 3), assay variability or inaccurate reference ranges (Pokrajac *et al.* 2007) can lead to false negative results, especially in mild cases.

The serum GH concentration measured during an oral glucose tolerance test (OGTT) is the gold-standard diagnostic test (showing the lack of normal suppression of serum GH concentration during hyperglycemia) and should be used to confirm the diagnosis in all cases with high or equivocal IGF1 or in situations possibly interfering with IGF1 measurement. The cutoff for nadir GH during OGTT is highly dependent on the assay used. With the use

Table 3 Tests used for the biochemical diagnosis of acromegaly. Data from Irie & Tsushima (1972), Clemmons & Van Wyk (1984), Duncan & Wass (1999), Hall *et al.* (1999), Freda *et al.* (2003), Arafat *et al.* (2008), Cordero & Barkan (2008), Frystyk *et al.* (2010), Minuto *et al.* (2012) and Katznelson *et al.* (2014)

Test	Normal values	Comments
OGTT Give 75 g glucose orally to a fasting patient Measure serum GH at baseline, 30, 60, 90, and 120 min	Suppressed GH levels: nadir below $<0.3 \mu\text{g/l}$ when using a highly sensitive GH assay Nadir GH $<1 \mu\text{g/l}$ acceptable with most assays	Possible abnormal results in females, obese patients catabolic states
Mean GH day curve Five-point curve of serum GH during the day	<1 and $2.5 \mu\text{g/l}$ for minimum and mean GH values	Difficult, time-consuming Rarely used
IGF1 No test preparation needed Sample can be taken at any time	Age- and sex-matched reference ranges are needed Preferably use the same kit/lab for the evaluation of the same patient	Inter-assay variability Influenced by age (\downarrow with age), sex (\downarrow in women), pregnancy (\uparrow), nutritional status (\downarrow in malnutrition), liver and renal failure (\downarrow), and glucose metabolism (\downarrow in DM)
TRH test 200 mg of TRH intravenously Serum GH measurement at 0, 20, and 60 min	Suppressed GH levels	Paradoxical rise (50% or more of the basal GH levels) in ACM Rarely, if ever, used today

\downarrow , Decrease; \uparrow , increase.

of ultrasensitive GH immunoassays, in healthy individuals the GH suppresses to very low levels after a 75 g glucose load (as low as 0.14 µg/l; Freda *et al.* 1998a). However, using such a low cut-off would only be applicable to ultrasensitive GH assays. Therefore, the current guidelines suggest that, because many GH assays currently used worldwide do not have adequate accuracy at low GH levels, a cutoff for nadir GH during OGTT below 1 µg/l is acceptable for excluding the diagnosis (Katznelson *et al.* 2014). However, it should be borne in mind that using this cutoff could lead to the inaccurate exclusion of the diagnosis in a significant percentage of cases with mild active disease (Dimaraki *et al.* 2002, Freda *et al.* 2003). Indeed, many cases of active mild ACM exhibit significant GH suppression during OGTT, as low as 0.33 µg/l (Freda *et al.* 1998b).

The mean value of several samples taken a few hours apart throughout the day can also be used (GH day curve (GHDC)) as it is significantly correlated with the GH nadir during OGTT (Dobrashian *et al.* 1993) and with the IGF1 level (Minuto *et al.* 2012). In normal subjects GH levels are usually undetectable, except for several pulses of secretion (mostly during the night; Duncan & Wass 1999, Peacey *et al.* 2001). In ACM, nadir GH levels during a day-curve do not suppress below 1 µg/l (as in normal subjects) and mean integrated 24-h levels are significantly elevated (Ho & Weissberger 1994), but the procedure is cumbersome and rarely used.

Further complicating the diagnosis in cases with mildly active disease (who could derive a great benefit from an early diagnosis and treatment) are the frequent (around 30% of cases) discrepancies between the GH and IGF1 hypersecretion. Elevated IGF1 with normal GH status may reflect earlier disease (Dimaraki *et al.* 2002) and should prompt a thorough investigation (including imaging) to clarify the diagnosis.

The major binding protein of IGF1, IGFBP3 is not useful for diagnosis or treatment follow-up as significant overlap occurs between normal controls and patients (Wass 1997).

In the rare situation where a non-pituitary aetiology is suspected, the serum GHRH level should be measured; GHRH secretion is responsible for 0.5% of all cases (Losa & Von Werder 1997).

PRL serum level should also be measured, as PRL may be co-secreted with GH in up to a third of patients (Reddy *et al.* 2010). Also, once the diagnosis is secured, a thorough investigation of the pituitary function should be performed.

Imaging

Once the biochemical diagnosis of ACM is made, the documentation of the responsible PA (the most common cause of ACM), its appearance and involvement of the parasellar structures by contrast-enhanced magnetic resonance imaging (MRI) or, when contraindicated or not available, computed tomography (CT)-scan is required (Katznelson *et al.* 2014). At diagnosis, most ACM patients have a macroadenoma (73% in a national registry study (Mestron *et al.* 2004)), sometimes with extrasellar extension. The tumor usually appears hypointense on T1-weighted MRI and has decreased contrast-enhancement compared to the surrounding normal tissue. The hyperintense appearance on T2-weighted MRI frequently corresponds to more aggressive SG tumors (Hagiwara *et al.* 2003). In contrast, the hypointense T2-weighted signal on MRI is indicative of increased SSA responsiveness (Puig-Domingo *et al.* 2010).

Additional testing

Visual field assessment should be done in all cases of macroadenoma close to the optic chiasm (Katznelson *et al.* 2014). Also, assessment of the pituitary function and proper replacement of any deficient axes are mandatory. Evaluating for most frequent comorbidities is recommended at diagnosis. Once the diagnosis of ACM is confirmed, a baseline colonoscopy and thyroid ultrasound are recommended; cardiological assessment including echocardiography or Holter EKG exploration are indicated if clinical findings are suggestive of cardiovascular complications (Katznelson *et al.* 2014).

Treatment

Overview

Treatment of ACM is complex and aims to control symptomatology, normalize the hormonal excess and decrease the risk of complications, shrink or completely remove the pituitary mass with minimal impairment of the normal pituitary function. Treatment methods include surgery, medical treatment, and adjuvant RT. IGF1 levels are promptly normalized after successful surgery or medical treatment (either with SSA (Lamberts *et al.* 1988) or PEG (Trainer *et al.* 2000)) and this is correlated with improvement of the signs and symptoms of the disease (Clemmons *et al.* 1979).

Selective transsphenoidal adenomectomy is usually the first-line treatment, especially in those with fully

resectable tumors or with visual impairment (Giustina *et al.* 2000). Medical treatment with SSA is usually initiated in persistent disease after surgery; it can also be used in selected cases as first-line treatment. With the progressive development of efficacious, better-tolerated drugs, RT is falling out of favor, being reserved to cases resistant to other therapies.

Surgery

The surgical intervention aims to completely remove the PA while preserving or restoring the pituitary function. Transsphenoidal surgery using either the endoscopic or microsurgical approach is the gold standard. Some studies report substantially better outcomes for the endoscopic approach (Dorward 2010), while others find no significant difference in remission rates (Starke *et al.* 2013), so the choice between them currently depends on the preference and expertise of the surgical team. Craniotomy is very rarely used.

Although the surgical results have overall improved in the last decades (Bates *et al.* 2008), the experience of the surgeon is still essential for surgical cure (Bates *et al.* 2008, Schofl *et al.* 2013). In older series, disease remission using milder criteria (defined as normal IGF1 and/or nadir GH below 2 µg/l) was achieved in 61% of cases overall (88% for microadenomas) (Freda *et al.* 1998b). When using current biochemical remission criteria (see below), the best reported rates for micro- and macroadenomas were 81–100% and 45–68% respectively (Ludecke & Abe 2006, Jane *et al.* 2011, Sun *et al.* 2014). In a large study based on the German ACM Registry, reflecting the integrated results obtained by different centers, the overall rate of IGF1 normalization by surgery alone was only 38.8% (Schofl *et al.* 2013).

The chance of remission is inversely correlated with tumor dimension, preoperative GH/IGF1 level, number of operations (Sun *et al.* 2014), age (Abosch *et al.* 1998), and invasion of adjacent structures – cavernous sinus invasion indicates a tumor not fully resectable (Nomikos *et al.* 2005) – and early postoperative GH level (Freda *et al.* 1998b). In one study, male sex and parasellar extension (especially cavernous sinus invasion) were the most powerful predictors for persistent disease (van Bunderen *et al.* 2013).

Presurgical SSA administration has been reported to improve surgical outcome and reduce complications (Annamalai *et al.* 2013), but these findings were not confirmed by other authors (Losa *et al.* 2006). Randomised controlled studies exploring the potential benefits are scarce (Carlsen *et al.* 2008, Mao *et al.* 2010, Shen *et al.* 2010,

Fougner *et al.* 2014). All involve small series treated for a few months before surgery. Immediate results of surgery are significantly better in pretreated cases (Carlsen *et al.* 2008, Mao *et al.* 2010, Shen *et al.* 2010), but the long-term results are conflicting: some authors report no difference (Shen *et al.* 2010) while others report a slightly higher cure rate in the pretreated group at 5 years follow-up (41% vs 27%) (Fougner *et al.* 2014). In a recent meta-analysis, the chance of surgical remission (GH nadir after OGTT <1 µg/l and normal age-matched IGF1) was overall higher in pretreated patients (Nunes *et al.* 2015). However, the extent and quality of the currently available evidence supporting the routine use of presurgical SSA are low, so it is not recommended as a routine approach (Katznelson *et al.* 2014). It can be used for specific patients (invasive macroadenomas with low probability of surgical cure, severe complications) for a few months (Melmed *et al.* 2009, Jacob & Bevan 2014, Katznelson *et al.* 2014). SSA pretreatment can also be useful in individual patients with severe soft tissue overgrowth (associated with intubation difficulties and complications) as it reduces the anesthetic complications and facilitates intubation (Friedel *et al.* 2013).

Surgical debulking also improves later control by SSA (Wass 2005, Karavitaki *et al.* 2008; not unexpected, as responsiveness to SSA is inversely correlated with pretreatment disease burden; Bhayana *et al.* 2005). Therefore, surgery is indicated also in cases deemed surgically incurable at diagnosis, in order to improve the response to medical treatment (Katznelson 2010).

In addition to the increased chance of cure in experienced surgical centers, surgery also provides a tumor sample for pathological and immunohistochemical examination. Complications of surgery are usually minor (nasal congestion, sinusitis, epistaxis, and taste or smell abnormalities). Cerebrospinal fluid leak can occur in 2–5% of the cases (Nomikos *et al.* 2005, Tabaee *et al.* 2009). Major complications (meningitis, visual impairment, and carotid artery injury) occur in <1% of the cases in experienced pituitary centers. Mortality is reported in about 0.1% of the cases operated in dedicated centers (Nomikos *et al.* 2005). The pituitary function is improved in almost half of the operated cases. Worsening of the pituitary function is reported in a minority of cases operated transsphenoidally but occurs in a quarter of those rare cases approached transcranially (Nomikos *et al.* 2005). Diabetes insipidus (DI) can occur in a minority of patients, mostly transient, with <2% chance of permanent DI (Abbassioun *et al.* 2006, Tabaee *et al.* 2009).

The long-term recurrence rate following apparent successful initial surgery is generally low (0.4–1.1%; Kreutzer *et al.* 2001, Nomikos *et al.* 2005), but in some series recurrence rates of 10% at 15 years have been reported (Swearingen *et al.* 1998), probably reflecting the inherent low growth rate of small unresected remnants. Recurrences peaked between 1 and 5 years after surgery. A low postoperative hormone concentration is correlated with a decreased recurrence risk (Roelfsema *et al.* 2012). Patients with remission should be reevaluated yearly, and those with persistent disease should receive medical treatment (Katznelson *et al.* 2014).

In view of its lower comparative costs, low complications rates and reasonable efficacy, surgery remains the recommended primary treatment method in most patients (Katznelson *et al.* 2014).

Medical treatment

Medical treatment is currently a mainstay of the complex treatment of ACM. A large body of evidence proves its efficacy, with various response rates depending on the preparation, regimen used, patients characteristics and so on.

SS analogs SSA are analogs with longer half-life of the endogenous SS, acting on the SS receptors (SSR) in the pituitary. The SSR belong to a family of G-protein-coupled receptors with five members described (SSR1–5). GH-secreting PAs frequently express SSR (mostly type 2; Hofland & Lamberts 2001). Through their specific interaction with these receptors, SSA exert antisecretory and antiproliferative effects.

The SSA in use are octreotide (OCT) and lanreotide (LAN). Initial OCT formulations (administered as three daily s.c. injections) proved useful, resulting in significant symptoms improvement and hormonal response in most cases (Newman *et al.* 1995). Currently long-acting SSA formulations are available (OCT long-acting release (OCT-LAR), LAN sustained release (LAN-SR), and LAN autogel (LAN-ATG)), and they represent the first-choice medical treatment. The reported efficacy differs among various studies, but there is also marked heterogeneity related to treatment algorithm, case selection and definition of remission; also, most studies lack a control arm.

As the surgical cure rates are still low in many GH-secreting macroadenomas, postsurgical SSA are mainly indicated in cases with persistent disease after surgery (Katznelson *et al.* 2014). Overall, OCT-LAR reduced GH to below 2.5 µg/l and normalized the IGF1 levels in 66 and

63% of cases, respectively, in a critical analysis of the largest studies (Murray & Melmed 2008). The same targets were achieved with LAN-SR in 52 and 47% of cases respectively (Murray & Melmed 2008). In an earlier meta-analysis, the overall chance of IGF1 normalization was 67% with OCT and 47% with LAN-SR (Freda *et al.* 2005). Although LAN-SR appears slightly less efficacious, there are several important caveats to be accounted for (inclusion of both primary and secondary treated cases, unclear dose optimization protocols, small number of cases in the studies included). Also, some of the cases included had been preselected for SSA responsiveness. Preselection of responsive cases is usually based on prior use, but the OCT suppression test (hourly GH measurements for 6 h following 100 µg s.c. OCT) has also been suggested. The overall predictive power of the test is, however, suboptimal. The nadir GH during OGTT is correlated with safe GH and IGF1 during OCT-LAR but less so for LAN (Karavitaki *et al.* 2005). Also, the tumoral response under SSA is only modestly correlated with the OCT test (Annamalai *et al.* 2013).

As expected, the preselection is associated with higher IGF1 normalization and tumor shrinkage rates (Freda *et al.* 2005). Consequently, in unselected cohorts the rate of biochemical control was lower: 44% of cases treated with OCT-LAR reach GH <2.5 µg/l and 34% a normal IGF1 after 48 weeks (Mercado *et al.* 2007).

With long-term SSA administration, a gradual further improvement can be expected, with maximal benefit achieved after more than 10 years of treatment (Maiza *et al.* 2007). In a large national-registry-based analysis, 'safe' (<2 µg/l) GH levels were achieved with long-term SSA treatment in 75%, normal IGF1 in 69% and both in 55% of cases. Adenomas with a DG cytokeratin pattern (Larkin *et al.* 2013), high SSR2 and SSR5 expression (Espinosa de los Monteros *et al.* 2014), low Ki-67 index (Kasuki *et al.* 2012), as well as those previously subjected to surgery and/or RT (Howlett *et al.* 2013) respond better to SSA treatment.

Biochemical remission is the most important effect, but tumor shrinkage also occurs. Published meta-analyses revealed that OCT-LAR (Giustina *et al.* 2012) and LAN formulations (Mazziotti & Giustina 2010) induce some degree of tumor shrinkage in 66.0 and 32.8% of cases respectively. Fifty-seven percent of patients treated with OCT exhibit tumor shrinkage of at least 20%; the mean computed degree of change induced by OCT-LAR was around 50% (Giustina *et al.* 2012). In isolated cases the shrinkage effect can be spectacular (Espinosa de los Monteros *et al.* 2014). Tumor decrease is more

frequent and significant in primary-treated patients and in large macroadenomas (Mazziotti & Giustina 2010, Colao *et al.* 2011).

The use of SSA as primary treatment was also advocated as it proved to be efficacious in uncontrolled studies (Cozzi *et al.* 2006). As primary treatment, SSA induce a clinically significant degree of tumor shrinkage in 36% of cases; the mean calculated percentage of tumor reduction was about 50% in these responsive cases. If all cases are taken into account, the overall tumor reduction is 19% (Melmed *et al.* 2005). Primary SSA treatment is associated with a lower remission rate compared to initial surgery (45% vs 67% for surgery; Abu Dabrh *et al.* 2014). To date, there are no robust data to support the routine recommendation of primary SSA treatment. It can be offered before surgery in patients with contraindications or who refuse surgery (Melmed *et al.* 2005), in cases with unresectable tumor (e.g., cavernous sinus invasion) or with severe complications (Katznelson *et al.* 2014).

The preference for one SSA over another is not currently substantiated. Biochemical control (Murray & Melmed 2008) and tumor shrinkage (Freda *et al.* 2005) appear slightly more frequently with OCT-LAR compared to LAN-SR. However, this evidence does not come from randomized head-to-head comparisons and is subject to a number of biases and limitations, as discussed above. Also, the two available LAN preparations (LAR and ATG) induce similar results (Murray & Melmed 2008). Recently the results of a phase III multicenter trial on the efficacy of an oral OCT formulation showed that switching from injectable SSA to the oral formulation effectively maintains disease control in the majority of cases (Melmed *et al.* 2015).

Withdrawal of SSA is possible in a small but distinct subset of patients, particularly in those who are very well controlled on relatively low doses administered at long intervals (Ramirez *et al.* 2012). At SSA discontinuation, tumor regrowth is possible within months (Ezzat *et al.* 1992).

In contrast, a significant minority of the patients do not achieve biochemical remission, even with long-term treatment. The variable SSR5 expression may explain the partial responsiveness to SSA in patients with adequate SSR2 density in the cell membrane (Cuevas-Ramos & Fleseriu 2014). In these cases, initiation of PEG or cabergoline treatment is recommended (Katznelson *et al.* 2014).

During SSA treatment, improvement of joint and soft tissue symptoms as well as headache and perspiration frequently occurs (Caron *et al.* 2004, Mercado *et al.* 2007).

Side effects are frequent but mostly of little severity. Abdominal discomfort is frequent, especially at the initiation of the treatment. Gallbladder sludge or gallstones are also common. Pancreatitis is rare (Neggers *et al.* 2007). SSA suppress plasma insulin levels and were initially thought to aggravate the glucose intolerance; however, the overall effect on glucose metabolism is not clinically significant (Breidert *et al.* 1995), probably because the effect on GH and consequently insulin resistance predominates. A meta-analysis published in 2009 confirmed that, despite the decrease of fasting insulin and possible alteration of glucose levels during OGTT, fasting plasma glucose and HbA1c do not change significantly, arguing against a clinically significant effect (Mazziotti *et al.* 2009).

Pasireotide In patients inadequately controlled by classic SSA (OCT and LAN), a new multi-SSR-targeted compound (pasireotide), with high affinity for all human SSR types except type 4 (Bruns *et al.* 2002), was investigated in clinical studies.

Both pasireotide (Petersenn *et al.* 2014a) and pasireotide LAR (Petersenn *et al.* 2014b) appear promising as medical agents with antisecretory and antitumoral effect. A comparison between pasireotide LAR 40 mg/28 days and OCT-LAR 20 mg/28 days revealed that biochemical control (GH <2.5 µg/l and normal IGF1) after 12 months was achieved in significantly more cases treated with pasireotide LAR than with OCT-LAR (31% vs 19%). However, this study had no robust protocol for dose up-titration, and many patients in both groups did not receive a dose increase, altering the conclusion that can be drawn from the study (Colao *et al.* 2014).

Similar rates of biochemical control (27%) were reported with pasireotide after 3 months of treatment; 39% of the cases also had a significant (>20%) decrease in pituitary tumor volume (Petersenn *et al.* 2010). In the study of Colao *et al.* (2014), almost 80% of the cases treated for 1 year with either pasireotide or OCT LAR achieved a significant tumor decrease (mean reduction 40%), both postsurgical and *de novo* treated cases.

Pasireotide proved beneficial in a significant minority of patients uncontrolled by SSA: 15 and 20% of the cases treated with pasireotide LAR 40 and 60 mg, respectively, achieved biochemical control after 24 weeks in a large multicentric study (PAOLA; Gadelha *et al.* 2014).

However, hyperglycemia was recorded in 31–57% of the cases evaluated in these two studies (Colao *et al.* 2014, Gadelha *et al.* 2014). Currently pasireotide has not entered into clinical use.

Pegvisomant PEG is a GH receptor antagonist which blocks the peripheral synthesis of IGF1 (Muller *et al.* 2004). Initial trials demonstrated normalization of serum IGF1 concentration in 97% of the cases treated for at least 12 months (van der Lely *et al.* 2001). In real-life conditions the response rates are lower. In a worldwide surveillance study (Acrostudy) of patients treated only with PEG in daily s.c. injections, IGF1 was normalized in only 67.5% of cases after 3.8 years follow-up (Freda *et al.* 2014). The efficacy increases slightly with time (Schreiber *et al.* 2007), reaching 70.9% after 6 years (Grottoli *et al.* 2015). The response is dose-dependent: 89% of cases treated with 20 mg PEG daily reach a normal IGF1 in 12 weeks (Trainer *et al.* 2000). In clinical practice upward dose titration is not always offered to cases with partial response to lower doses (Freda *et al.* 2014), and this might explain suboptimal response rates. With a more stringent dose titration protocol 95% of the cases treated for a median duration of 18 months can achieve IGF1 normalization under current clinical care (Higham *et al.* 2009).

IGF1 normalisation is the main endpoint of treatment; GH levels increase during treatment and cannot be used for monitoring (van der Lely *et al.* 2001). Also, PEG does not have an anti-tumoral effect, and initially there was concern about the risk of tumor growth during treatment. However, tumor increase is a rare event, occurring in only 2.2% of cases (Freda *et al.* 2014).

The biochemical response to PEG leads to a significant decrease of symptomatology (especially at doses higher than 15 mg daily; Trainer *et al.* 2000). In contrast to SSA, PEG decreases fasting plasma glucose (Urbani *et al.* 2013) and improves glucose tolerance (Colao *et al.* 2006) and insulin sensitivity (Schreiber *et al.* 2007). Switching from SSA to PEG significantly improves diabetes control in diabetic ACM cases (Barkan *et al.* 2005). However, an indirect effect of the removal of previous SSA treatment in SSA-resistant cases can contribute to this result.

PEG is usually administered as daily s.c. injections; weekly or twice-weekly dosing (median doses 60 mg weekly) is another effective option though not currently in use (Neggers *et al.* 2009). It is generally well tolerated, with adverse reactions in <10% of cases (increases in liver enzymes, injection site reactions, and headache; Schreiber *et al.* 2007). With combined SSA-PEG treatment for 4.5 years, transaminase levels increased in 27% of cases (Neggers *et al.* 2009). However, with careful, continuous monitoring, the combined PEG-SSA treatment is widely used and highly effective: PEG added to patients uncontrolled by maximal doses of SSA normalize IGF1 in 95% of cases (Neggers *et al.* 2009).

PEG treatment is currently recommended in cases resistant or intolerant to SSA treatment (Herman-Bonert *et al.* 2000) or in combination with SSA in partially resistant cases (Katznelson *et al.* 2014). PEG is not currently used routinely as primary medical treatment but can be considered for this use in selected cases. For instance, in ACM patients with severe DM, its use could be safer due to its favourable impact on glycemic control (Barkan *et al.* 2005).

Dopamine agonists Dopamine agonists (DA) are efficacious in a subset of ACM patients, especially those with only mild GH hypersecretion (Howlett *et al.* 2013). Their use in the treatment of ACM has consistently declined in the last two decades, in parallel with the more frequent use of other medical options. Therefore, many patients currently treated with DA are those with proven responsiveness to this class of drugs before the widespread use of other drugs. This explains the higher rate of efficacy in current analyses. The large heterogeneity of the regimens used also adds to the difficulty in assessing the outcome. With these biases in mind, long-term DA treatment achieved 'safe' GH levels in 50%, normal IGF1 in 36%, and both in 26% of the cases evaluated after 2000 (Howlett *et al.* 2013), a roughly similar percentage of success to that achieved by SSA. In a systematic review assessing the efficacy of cabergoline in ACM, the overall rate of normalization was 34%. When added to SSA (in patients with suboptimal control), 52% of the cases achieved normal IGF1 levels (Sandret *et al.* 2011). When added to PEG, cabergoline normalize IGF1 in 28% of cases with partial response (Bernabeu *et al.* 2013). Consequently, the use of cabergoline is recommended in patients with inadequate response to other medical forms of treatment, and the highest benefit is expected in cases with modest persistent hormonal elevations (Katznelson *et al.* 2014). The commonly held view that DA are more effective in PA with mixed GH-PRL secretion is not supported (Cozzi *et al.* 2004, Sherlock *et al.* 2009).

Cardiac valve impairment secondary to cabergoline use was described in long-term use of high doses (recommended for Parkinson's disease) but not in cases treated with routine endocrinological doses (Samson & Ezzat 2014).

Other treatment options **Estrogens** The addition of estrogens or selective estrogen receptor modulators (SERM) to the treatment was reported to offer additional benefit, with greater reduction in IGF1 for estrogens compared to SERM (Stone *et al.* 2014). Concurrent use of

estrogens in ACM is not recommended by the current guidelines, therefore their use can only be considered by individual medical judgement in selected female patients (especially resistant to other available therapies) after a thorough evaluation of all possible risks and contraindications.

Other options Trials are under way to assess the efficacy and safety of several other molecules or formulations: new SSA (targeted at more receptors types), chimeric molecules, with specificity for both SSR and dopamine receptors (dopastatins), and oral delivery of currently used SSA (Cuevas-Ramos & Fleseriu 2014). In the future these alternative drugs could become clinically available, expanding the therapeutic armamentarium.

Radiotherapy The benefits of RT (tumor shrinkage and decreased hormonal secretion) must be weighed against the long latency of the effect and the high risk of adverse effects, especially pituitary dysfunction. As new, effective medical options with less side effects appeared, RT has fallen out of favor and is currently reserved for patients with persistent disease despite surgery and/or medical treatment or if medical treatment is not tolerated or unavailable (Katznelson *et al.* 2014).

Conventional fractionated RT (mean doses of 45–50 Gy) is associated with a very slow onset of effects (5–15 years until maximal benefit), but eventually the tumor control is about 95% (Minniti *et al.* 2005a) and the biochemical response reported in series with long-term follow-up (up to 20 years) is very good: 60–77% (Biermasz *et al.* 2000, Minniti *et al.* 2005a, Jenkins *et al.* 2006). However, very high rates of new hypopituitarism (77%) are reported (Minniti *et al.* 2005a). With long (more than 10 years) follow-up, in some series almost all patients developed hypopituitarism (Littley *et al.* 1989, Langsenlehner *et al.* 2007). Newer stereotactic techniques (single-dose stereotactic radiosurgery (SRS) fractionated stereotactic RT) have improved efficacy and reduced the frequency of side effects due to the more localized delivery of radiation (Minniti *et al.* 2012). SRS can be given either by linear accelerator or by cobalt unit (gamma-knife (GK)). The rates of both biochemical and tumor response are very variably reported in the literature: 17–82% and 37–100%, respectively, as reported in a critical analysis of the literature (Stapleton *et al.* 2010). This high variability can be attributed to different treatment schedules, criteria of cure or follow-up durations. GK treatment induces tumor shrinkage in about 60–75% of cases (Jezkova *et al.* 2006, Lee *et al.* 2014a) at 5–6 years and the percentage continues

to increase slowly up to 82% at 8 years (Lee *et al.* 2014a). The biochemical control rate is more difficult to be appreciated because various control criteria were used; a crude estimate from the largest studies published suggest biochemical control with GK in about 48% after a mean follow-up of 4 years (Newell-Price 2009).

The use of SSA possibly decreases the success of SRS (Pollock *et al.* 2002), so temporary interruption of the medical treatment before RT is suggested. In contrast, in the interval until RT becomes efficacious, the use of SSA is recommended (Melmed *et al.* 2009).

The prevalence of hypopituitarism with stereotactic techniques is considerably lower. Overall radiation-based treatment in mixed series induces hypopituitarism in almost half of the patients over a long follow-up (Jallad *et al.* 2007). In cohorts treated solely with stereotactic methods variable rates of hypopituitarism have been reported from below 10% at 3.8 years (Attanasio *et al.* 2003) to 31% at 8 years (Lee *et al.* 2014a), 12–20% in most series (Milker-Zabel *et al.* 2001, Pollock *et al.* 2002, Wilson *et al.* 2013), especially in large tumor masses (Pollock *et al.* 2002, Beauregard *et al.* 2003). Owing to the possibility of late hypopituitarism, long-term follow-up and periodic testing are mandatory after RT.

Apart from hypopituitarism, other major complications are possible following RT. Second brain tumors have been described long before exposure (2–30 years) in 2.4% of cases (Minniti *et al.* 2005b). The prevalence of cerebrovascular accidents increases with time from exposure: 4% at 5 years, 11% at 10 years, and 21% at 20 years (Brada *et al.* 1999). Rarer occurrences are optic neuropathy (also occurring about 15 years after irradiation in 1–2% of cases; Fernandez *et al.* 2009) and brain necrosis – an exceptional side effect. As most of these complications become apparent many years after the irradiation, more data are available about conventional RT. Prolonged follow-up of patients who underwent stereotactic RT in the last decades will clarify the risks following these procedures. Rare complications of SRS are cranial nerves deficits, headache, radiation necrosis, carotid artery stenosis, and trigeminal neuralgia (Beauregard *et al.* 2003, Stapleton *et al.* 2010). The risk of visual complications limits the use of SRS to lesions more than 3 mm away from the optic structures (Petrovich *et al.* 2003). To date, if RT is indicated, stereotactic methods should be applied, unless the tumor remnant is large or close to the optic apparatus (Katznelson *et al.* 2014).

Favorable prognostic factors for remission included a higher margin radiation dose, higher maximum dose and lower initial IGF1 level (Lee *et al.* 2014a). The remission

rates are similar in SG and DG tumors. For SG adenomas, which respond less well to medical therapy, earlier SRS may be reasonable for consideration (Lee *et al.* 2014b).

Follow-up under treatment

The real efficacy of the treatment in ACM is difficult to be interpreted due to the variability in the assays used, follow-up interval, definition of biochemical response as well as the inclusion of both naïve and preselected prior responders. Overall, in real-life conditions, the data from the large UK register suggest that only 75% of the cases receiving medical GH-lowering treatment (SSA and/or DA) are adequately controlled (Howlett *et al.* 2013).

The best test used to assess the disease status also depends on the treatment offered to the patient. In the first 3 months after surgery GH suppression is more useful than IGF1 in predicting remission (Feelders *et al.* 2005); immediately after surgery OGTT or GHDC can be performed, with OGTT being more cost-efficient (Karavitaki *et al.* 2009). Also, a morning fasting GH sample has a very good positive predictive value for disease cure or control (Karavitaki *et al.* 2009). A fasting GH below 2 µg/l on the first postoperative day is predictive for remission (Krieger *et al.* 2003).

In patients receiving SSA, OGTT is not useful in assessing biochemical control. In these patients, both basal and post-glucose GH levels are highly discordant with serum IGF1 concentrations (Carmichael *et al.* 2009). A random GH or mean GHDC can be used (Giustina *et al.* 2010), and normalization of IGF1 is an essential marker of biochemical control in SSA-treated cases (Katznelson *et al.* 2014).

During treatment with PEG, no direct measure of GH secretion is useful (due to possible increase of secretion as a result of negative feedback, as well as cross-reactivity between the drug and some diagnostic assays; Muller *et al.* 2004). Instead, IGF1 normalization is the only marker of disease control (Giustina *et al.* 2010).

Defining cure/remission

The biochemical definition of disease remission or cure is difficult: nadir GH during OGTT, mean GH during GHDC and IGF1 have been widely used but with many problems related to the assay, reference ranges or cutoffs used. As the definitions are still controversial, it is essential to maintain, whenever possible, the same biochemical assays throughout the management of an individual patient (Katznelson *et al.* 2014).

Optimal disease control is currently defined as normal age-adjusted IGF1 level and a random GH <1 µg/l or nadir GH in OGTT <0.4 µg/l (Giustina *et al.* 2010, Katznelson *et al.* 2014). Active disease is biochemically characterized by random GH >1 µg/l and nadir GH in OGTT ≥0.4 µg/l with elevated IGF1 (Giustina *et al.* 2010).

The cutoff for the nadir GH is highly assay-dependent; when highly sensitive assays (now more readily available worldwide) are used, up to 50% of patients with active ACM have nadir GH values below 1 µg/l (Freda *et al.* 1998a). Some authors proposed a 0.25 µg/l cutoff to differentiate the persistent disease activity (Serri *et al.* 2004). An even lower cutoff was advocated by some authors who reported that 25% of postsurgical cases with normal IGF1 and nadir GH >0.14 µg/l experienced recurrence (Freda *et al.* 2004). If such very low cutoffs for nadir GH are used, only a minority of treated cases can be declared cured (Freda *et al.* 1998a), and in this group hypopituitarism is more likely (Costa *et al.* 2002). Less stringent endpoints might be better related to normal age-matched IGF1 concentrations (Costa *et al.* 2002) and also have meaningful effects in terms of disease-related morbidity and mortality. Mean basal GH levels below 2.5 µg/l and normal IGF1 levels restore the SMR to that of healthy controls (Bates *et al.* 1993, Orme *et al.* 1998, Holdaway *et al.* 2003). Therefore, in clinical practice, aiming for 'safe' values, such as those recommended by the current guidelines, is more realistic.

Further complicating the matter is the frequent occurrence of discordant GH and IGF1 levels after or during treatment (Wass 1997, Carmichael *et al.* 2009). The significance and natural history of these cases is not fully understood. In many (39%) cases with normal IGF1, the GH suppression in OGTT is abnormal if assayed with a highly sensitive assay (Freda *et al.* 1998a). Some of these cases are the result of persistent dysregulation of GH secretion (Ho & Weissberger 1994) leading to minor GH elevations which do not uniformly increase the IGF1 concentration (Clemmons 2005). In others, persistent elevations of GH despite normal IGF1 are associated with a higher recurrence risk (Freda *et al.* 2004). Also, very low GH but elevated IGF1 can be encountered in persistent disease (Freda 2003). In cases with discrepant results, GHDC could be useful (Melmed *et al.* 2009, Giustina *et al.* 2010).

Disease control is not always associated with optimal control of the complications, despite overall improvement and decrease in mortality (Holdaway *et al.* 2003). For instance, in the presence of discordant serum IGF1 and nadir GH levels, IGF1 is more predictive than GH levels of

insulin sensitivity and clinical symptom score (Puder *et al.* 2005). It is also not clearly established whether both GH and IGF1 cutoffs are necessary to normalize mortality. In one analysis both random serum GH $<2.5 \mu\text{g/l}$ or a normal adjusted IGF1 level following treatment were associated with mortality close to expected levels (SMR 1.1; Holdaway *et al.* 2008). In contrast, the effect of IGF1 could not be demonstrated by other studies (Sherlock *et al.* 2010). It remains unclear whether the control of GH, but not IGF1, observed in many patients, is sufficient to restore long-term morbidity and mortality to normal.

Long-term results of the treatment

With complex, combined treatment (see Fig. 1), 75–94% of the cases are controlled according to current criteria (Biermasz *et al.* 2004, Abbassioun *et al.* 2006, Schofl *et al.*

2013). Disease control is associated with significant improvement of the symptomatology (Swearingen *et al.* 1998, Beauregard *et al.* 2003) and QoL (Caron *et al.* 2014). With IGF1 normalization, resolution of symptoms and partial improvement of specific ACM complications also occur (Clemmons *et al.* 1979, Holdaway *et al.* 2003). Glucose metabolism abnormalities are potentially reversible with successful surgery (Mori *et al.* 2013) or PEG treatment (van der Lely *et al.* 2001). Biochemical control is associated with a lower prevalence of DM (Reimondo *et al.* 2014), partial improvement of the cardiac dysfunction and increase in the cardiac performance (Mosca *et al.* 2013). Hypertension, valvulopathy (Colao *et al.* 2004), sleep apnea (Roemmler *et al.* 2012), joint complaints and related decrease in QoL (Biermasz *et al.* 2005) and overall affected QoL (Webb 2006) persist in a high percentage of patients with even controlled disease.

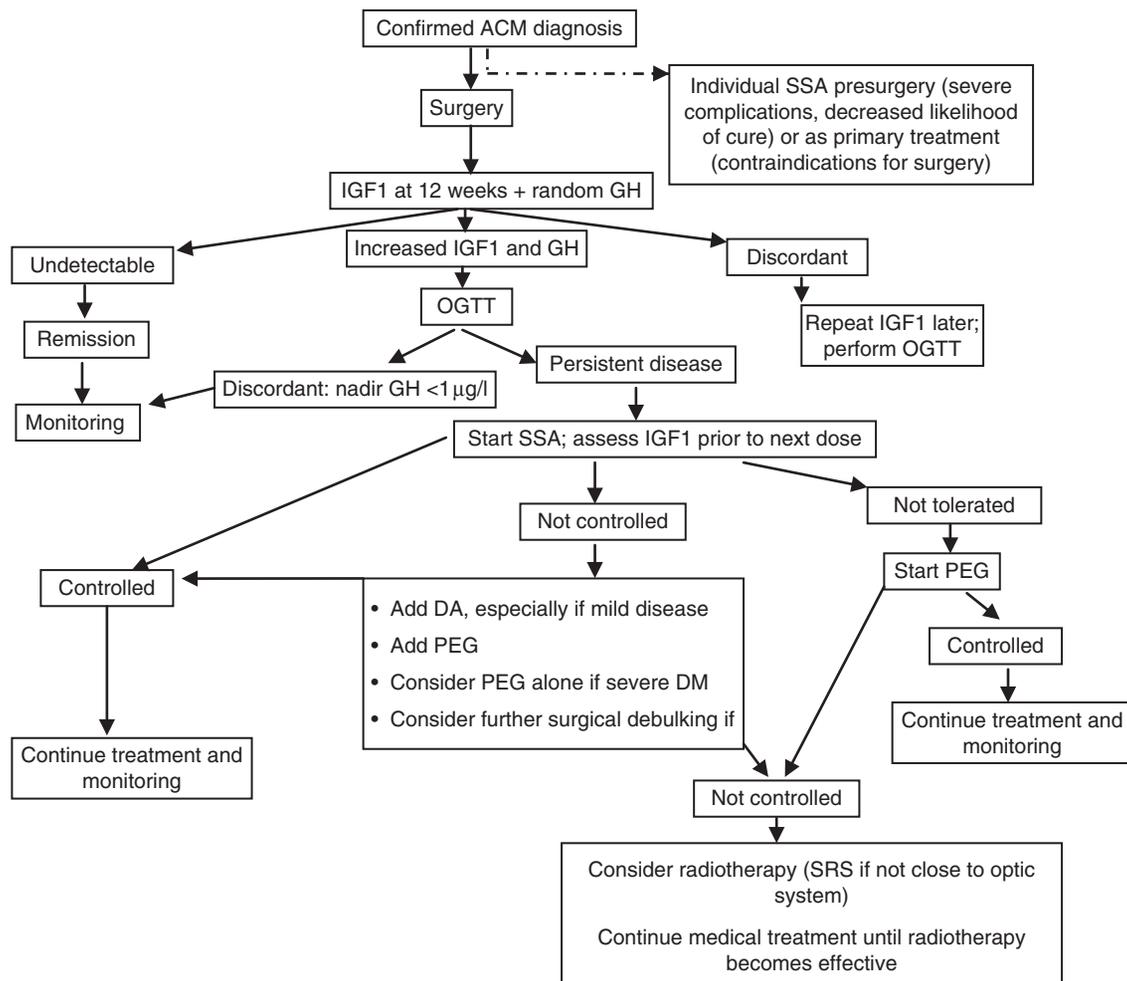


Figure 1
Algorithm of treatment in ACM.

The increased mortality associated with active, persistent disease returns to expected values in cured patients, while persistent disease is still associated with a SMR of 1.8 (Swearingen *et al.* 1998). High post-treatment GH levels are associated not only with an increased overall mortality rate but also increased mortality rates due to colon cancer, cardiovascular disease and all malignant disease (Orme *et al.* 1998).

Conclusions

Tight biochemical control of ACM is essential to reduce morbidity and to decrease the mortality rates to the level of the general population. Optimal implementation of current protocols in routine clinical practice and maximal use of the medical treatment options could improve the long-term control of patients with significant benefits for morbidity and mortality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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