

## CONSENSUS STATEMENT

**Consensus statement: medical management of acromegaly**

S Melmed, F Casanueva<sup>1</sup>, F Cavagnini<sup>2</sup>, P Chanson<sup>3</sup>, L A Frohman<sup>4</sup>, R Gaillard<sup>5</sup>, E Ghigo<sup>6</sup>, K Ho<sup>7</sup>, P Jaquet<sup>8</sup>, D Kleinberg<sup>9</sup>, S Lamberts<sup>10</sup>, E Laws<sup>11</sup>, G Lombardi<sup>12</sup>, M C Sheppard<sup>13</sup>, M Thorner<sup>11</sup>, M L Vance<sup>11</sup>, J A H Wass<sup>14</sup> and A Giustina<sup>15</sup>

*Cedar-Sinai Research Institute, UCLA School of Medicine, Los Angeles, USA, <sup>1</sup>Santiago de Compostela University, Spain, <sup>2</sup>University of Milan, Italy, <sup>3</sup>Hospital Bicetre, Paris, France, <sup>4</sup>University of Illinois, Chicago, USA, <sup>5</sup>University Hospital CHUV, Lausanne, Switzerland, <sup>6</sup>University of Turin, Italy, <sup>7</sup>Garvan Institute of Medical Research, Australia, <sup>8</sup>Université de la Méditerranée, Marseille, France, <sup>9</sup>NY University Medical Center, New York, USA, <sup>10</sup>University Hospital, Rotterdam, the Netherlands, <sup>11</sup>University of Virginia, Charlottesville, USA, <sup>12</sup>School of Medicine, Naples, Italy, <sup>13</sup>University of Birmingham, UK, <sup>14</sup>Radcliffe Infirmary, Oxford, UK and <sup>15</sup>University of Brescia, c/o 2<sup>o</sup> Medicina, Spedali Civili, Brescia 25125, Italy*

(Correspondence should be addressed to A Giustina; Email: a.giustina@libero.it)

**Abstract**

In November 2003, the Pituitary Society and the European Neuroendocrine Association sponsored a consensus workshop in Seville to address challenging issues in the medical management of acromegaly. Participants comprised 70 endocrinologists and neurosurgeons with international expertise in managing patients with acromegaly. All participants participated in the workshop proceedings, and the final document written by the scientific committee reflects the consensus opinion of the interactive deliberations. The meeting was supported by an unrestricted educational grant from Ipsen. No pharmaceutical representatives participated in the program planning or in the scientific deliberations.

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**Introduction**

During the natural course of acromegaly, cardiovascular, respiratory and metabolic co-morbidities contribute to significantly enhanced mortality. These systemic complications are linked to permanently elevated growth hormone (GH) and insulin-like growth factor (IGF)-I levels. Often, multi-modal therapies, including surgery, pharmacologic and radiotherapeutic, are required for disease control through suppression of GH hypersecretion, reduction of IGF-I levels and control of tumor growth. This statement reflects the Consensus achieved during the workshop held in November 2003 in Seville (list of participants reported in Table 1) on challenging issues facing physicians treating patients harboring GH-secreting pituitary tumors.

**Criteria for cure of acromegaly****Goals**

The goals of therapy in patients with acromegaly are the elimination of morbidities associated with the disease and normalization of the increased mortality. These are achieved by using safe treatments which ameliorate mass effects or remove the tumor mass and restore GH and IGF-I secretion to normal. Hypopituitarism should be avoided.

**Clinical criteria**

No single anthropometric parameter evaluable in patients with acromegaly correlates with control of GH and/or IGF-I secretion. Normalization of all comorbidities does not necessarily correlate with the therapeutic achievement of normal GH and IGF-I secretion. The age of the patient at diagnosis and the duration of disease prior to diagnosis have an impact on these factors. Therefore, clinical and biochemical assessment of the patient must be individualized.

**Biochemical criteria**

With current biochemical markers, it is inappropriate to ascribe the achievement of cure. With currently available treatments, normal GH secretion dynamics are only rarely achieved. It is therefore more appropriate to define disease control in these circumstances.

**GH**

Considerable advances have been made in recent years in GH assay technologies, but older epidemiologic data were derived from less sensitive polyclonal radioimmunoassays. More sensitive immunoradiometric assays show that disease activity occasionally persists after treatment if the Cortina criteria for cure are applied (1). Improved assay sensitivity now indicates that for control to be achieved the nadir GH level after oral glucose should be

**Table 1** List of meeting participants.

Giovanni Amato	Steven Lamberts
Ariel Barkan	Edward Laws
Paolo Beck-Peccoz	Alfonso Leal Cerro
Albert Beckers	Gaetano Lombardi
Bengt-Ake Bengtsson	Ernest Loumaye
Vivien S. Herman Bonert	Giulio Maira
Marco Boscaro	Franco Mantero
Pierre-Marc Bouloux	Josef Marek
Marcello Bronstein	Enio Martino
Thierry Brue	Shlomo Melmed
Michael Buchfelder	Francesco Minuto
Philippe Caron	Mark Molitch
Davide Carvalho	Hans Orskov
Felipe Casanueva	Stephan Petersenn
Francesco Cavagnini	Antonio Miguel Pico Alfonso
Philippe Chanson	Hans-Jurgen Quabbe
Richard N. Clayton	Richard Ross
David Clemmons	Agnes Schonbrunn
Annamaria Colao	Michael C Sheppard
David Cook	Anna M Spada
Renato Cozzi	Gunter K. Stalla
Michael D. Culler	Christian J. Strasburger
Ettore C. Degli Uberti	Guido Tamburrano
Rudolph Fahlbusch	Massimo Terzolo
Lawrence A. Frohman	Michael Thorner
Rolf Gaillard	George Tolis
Ezio Ghigo	Peter Trainer
Andrea Giustina	Helen Turner
Yona Greenman	Aart Jan Van der Lely
Ashley Grossman	Mary Lee Vance
Irene Halperin Rabinovich	John A.H. Wass
Mark Hartman	Susan Webb
Ken Ho	
J. Larry Jameson	
Philippe Jaquet	
Paul Jenkins	
Laurence Katznelson	
Paul A. Kelly	
David Kleinberg	

considerably below 1 µg/l (2). Endocrinologists should be familiar with the more sensitive assays in use in their laboratories and the normal nadir values achieved with GH after oral glucose. Furthermore, more data are required with these assays to assess 'normality' in males and females. Therefore, for complete control of GH dynamics to be achieved, nadir values should be below 0.4 µg/l.

The oral glucose tolerance test is unreliable in diabetes mellitus where loss of normal GH suppression may be seen. There are no epidemiologic data on mortality or morbidity in acromegaly from these more sensitive assays.

### IGF-I

The attainment of normal IGF-I remains an important goal in the biochemical assessment of acromegaly treatment. The utility of most IGF-I assays is limited by lack of standardization; normal values should be age- and gender-matched. Information correlating the achievement of a normal mortality with normalization of

IGF-I levels is limited and conflicting, and more data are required. Measuring other GH-related peptides, such as ALS and IFG BP-3, may be helpful, as when GH and IGF-I levels are discordant, but their use is not routine or mandatory.

### Postoperative assessment

Both GH and IGF-I levels should be measured. During the oral glucose tolerance test (OGTT), GH and glucose should be measured from 0 to 120 min. When the patient has been administered long-acting somatostatin receptor ligands (SRLs) prior to surgery, this interval should be longer (at least 4 months). During an OGTT, GH should fall below 0.4 µg/l in a sensitive noncompetitive immunometric GH assay. There is some suggestion that higher nadir values portend a subsequent relapse. The IGF-I level measured 3 months after surgery should be in the age- and sex-matched normal range. The effectiveness of therapy is monitored by measuring IGF-I and assessing GH responses to oral glucose as above. The efficacy of all modalities of therapy, including surgery, medical treatment and radiotherapy, are inversely related to baseline GH and IGF-I levels.

### Choice of medical therapies

**Dopamine agonists** Dopamine agonists are orally available and less costly than other agents but only occasionally effective in selected patients, including those with modestly elevated pretreatment IGF-I levels. It is noteworthy that dopamine agonists lower not only GH, but also prolactin (PRL) levels. There is no consensus on whether every patient should be given a trial of these medications.

Some participants believe that a higher pretreatment PRL level increases the chance of response, but objective studies are contradictory. Although GH hypersecretion in the absence of hyperprolactinemia may respond to dopamine agonists, a properly controlled study is needed to answer this question.

### Somatostatin analogs

SRLs selectively activate pituitary somatostatin receptor subtypes (3). In long-term studies, these molecules are safe and effective. They produce GH and IGF-I suppression, relief of soft tissue symptoms and control of tumor growth. Dose titration or modifying the interval between doses of long-acting somatostatin analogs should be performed at 3-month intervals. IGF-I levels may continue to fall in the long term, and tumor size may be reduced over two or more years of therapy (4, 5). There is no evidence that any currently approved SRL is superior to the others, although different formulations have theoretical but not clinically proven advantages. Bi- (SSTR2 and 5) or tri-specific (SSTR2, 5 and D2) therapeutic molecules appear to have potential in improving outcome.

In order for any SRL to be determined to be superior to currently available formulations, a prospective, controlled, head-to-head study is required. Because there are few objective data, a decision on when to switch between different SRLs is made on a case-by-case basis. SRLs are associated only with generally transient gastrointestinal disturbances and the development of asymptomatic gallstones (of limited clinical significance) during the first 2 years of therapy (4).

### **Pegvisomant**

The GH receptor antagonist, pegvisomant, blocks peripheral IGF-I operation in almost all patients, and is indicated in patients who are inadequately controlled with other modalities, or in patients experiencing clinically significant drug side effects (6). Tumor size should be monitored at intervals, since the therapy is directed at blocking peripheral GH receptors, and not at treating the pituitary tumor. Tumor growth has been observed in a few patients, and it is unclear whether this is due to tumor natural history or drug effect. Serum transaminases should be measured at monthly intervals for the first 6 months of therapy.

### **Summary of pharmacotherapy**

Management of acromegaly requires monitoring of markers of disease activity such as GH and IGF-I and also follow-up and therapy for complications such as diabetes mellitus, hypertension, sleep apnea, cardiomyopathy and arthropathy (7). Do combined modalities of medical management improve outcome? Studies on the combined use of SRLs and pegvisomant should be forthcoming.

Thus, the principles determining medical treatment, either as primary or adjunctive choice, include the following:

- Markedly elevated PRL levels favor use of a dopamine agonist.
- An aggressive tumor mass that soon gives rise to compressive symptoms, such as visual field defects, requires a therapy known to reduce tumor size, such as SRLs, rather than pegvisomant.
- Severe headache may require a short-acting, subcutaneous, somatostatin analog preparation.
- After failed surgery, somatostatin analogs may be continued in patients with aggressive tumors when pegvisomant is started.

### **Presurgical treatment**

Pressure of compressive symptoms, acute visual disturbances or apoplexy with neurologic consequences are clear contraindications for delaying a surgical procedure.

Medical therapy prior to planned surgery is recommended in patients with restrictive comorbidities,

including congestive heart failure, cardiomyopathy, severe sleep apnea, respiratory or intubation problems, or other debilitating features of acromegaly. It is advised that this assessment be made by an experienced endocrinologist together with the anesthesiologist. The duration of presurgical treatment should be individually determined. However, there is insufficient evidence that presurgical medical therapy can reliably improve perioperative morbidity. Data on the effect of presurgical medical treatment with somatostatin analogs on surgical outcome are limited. The only subpopulation of patients for whom it may be of marginal benefit are those with well-encapsulated adenomas. The rarely encountered, mixed GH–thyroid-stimulating hormone (TSH)-secreting adenomas may benefit from presurgical treatment with SRLs to control thyrotoxicosis.

We need a randomized, prospective study comparing ultimate biochemical control in patients treated presurgically versus untreated presurgical patients. At present, due to an absence of data, there is no consensus on including pegvisomant in presurgical treatment.

The possibility that presurgical medical treatment 'masks' residual disease postoperatively should be kept in mind. The assessment of surgical outcome needs to be done at least 4 months after interruption of long-acting somatostatin analog treatment.

### **Considerations for primary medical therapy**

Primary medical therapy (defined as presumed indefinite, long-term medical control of tumor growth, and GH and IGF-1 levels) may be considered for selected patients with acromegaly (8). Data on the effects of long-term primary medical therapy are required. Currently, SRLs are recommended for primary medical therapy, and dopamine agonists can be considered in certain cases (PRL-cosecreting tumors, relatively low levels of GH, or microadenomas). Insufficient data exist to recommend pegvisomant for primary therapy. The effectiveness of primary medical therapy with regard to tumor size and GH and IGF-1 levels should be assessed initially at 3–6-month intervals, and if therapy is ineffective, or if tumor growth persists, surgical resection should be reconsidered.

The following categories of patients are considered candidates for primary medical therapy: those with no risk of visual impairment from the tumor, those who are poor candidates for surgery, those who decline surgery, those with tumors unlikely to be controlled by surgery (as in lateral cavernous sinus invasion), and those who require the preservation of intact pituitary function (especially fertility). Multidisciplinary expert input is required for this prospective clinical decision.

Improvements in the surgical management of invasive tumors are needed, and the implications of surgical debulking for subsequent medical control need to be studied.

### Radiotherapy or stereotactic radiosurgery

There are currently no data to support radiotherapy or radiosurgery for primary management of acromegaly. In patients who had unsuccessful surgery, the major indication for radiotherapy or radiosurgery is in patients not controlled by medical therapy. In selected patients, circumscribed postoperative tumor remnants may be successfully subjected to radiotherapy or stereotactic radiosurgery.

### Patient concerns

The cost of acromegaly treatments varies, depending on the type of therapy, the country and the method of health-care payment. Cost-effectiveness and cost-benefit are important considerations, and treatments must be individualized. The high cost for an individual patient may in fact be acceptable because the overall burden to the health system is low, since this is a very rare disease. Determination of the cost/benefit ratio must include the consequences of long-term outcomes of poor disease control and the incidence of subsequent complications. Informed patient choice of therapy or therapies must be considered.

As both physical and psychological parameters of life quality are impaired in patients with acromegaly, an assessment of quality of life should be an integral part of patient evaluation, before and after treatment. Effects of different treatments on quality of life have not been determined and should be assessed by both generic and disease-specific surveys. Patient-oriented support groups may be helpful for both patients and their families.

In general, medical treatments for acromegaly are safe and well tolerated; each therapy has its own potential side effects, which must be explained to the patient. Potential side effects are one of the determinants, but not the primary consideration, in treatment selection.

### Non-GH-lowering treatments

Comorbidities of acromegaly, particularly hypertension, diabetes and dyslipidemia, should be assessed at the time of diagnosis. These may not always improve with treatment of acromegaly and should be managed as in the general population.

Hypertension should be treated according to established guidelines. The use of angiotensin converting enzyme inhibitors is recommended for those patients with diabetes, impaired glucose tolerance, microalbuminuria and cardiac hypertrophy. Hypertension in patients who have received cranial irradiation should be treated aggressively because of the increased risk of cerebrovascular disease these patients. Diabetes should be treated in a standard manner. Carbohydrate tolerance generally improves with control of GH hypersecretion.

Dyslipidemia, persisting after treatment of acromegaly, should be treated with diet and conventional lipid-lowering drugs.

The best outcomes for patients with acromegaly are obtained when they are treated in a center that has an expert team with focus and experience in the management of patients with pituitary disorders.

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