Medical Management of Acromegaly

a report by Philippe Chanson

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Acromegaly is a rare disease due to growth hormone (GH) hypersecretion by a pituitary adenoma. The rheumatologic, cardiovascular, respiratory and metabolic consequences determine the prognosis, and their severity increases with the length and degree of GH hypersecretion.1 The prognosis of acromegaly also depends on the culprit pituitary tumour, which may cause a tumoural syndrome, with headache and/or visual disorders due to optic chiasm compression.

**Prognosis of Acromegaly**

If untreated, acromegalic patients have a 10-year life expectancy reduction, particularly due to cardiovascular and respiratory problems and an increased risk of neoplasms. In recent studies the standardised mortality ratio (SMR) ranged from 1.2 to 3.3.2–11 The most important predictive factor of mortality is the so-called ‘final’ post-therapeutic GH level. When <2.5µg/l, SMR is not significantly different from that of the general population, while it is between 1.4 and 2 when >2.5µg/l. One recent study demonstrated a significant trend for increased mortality when GH levels exceed 1µg/l.7 Few studies provided any support for the use of insulin-like growth factor 1 (IGF1) as a marker for long-term outcome.2,7,9,11 This was not confirmed by others.8,10

**Treatment Objectives**

The clinical aims are to relieve symptoms, reduce the volume of the pituitary tumour, to avoid its tumour relapse and to improve long-term morbidity. Recent epidemiological studies12 helped to refine the definitions of ‘cure’ and good disease control, which are now far more precise. In a recent consensus statement, criteria for cure of acromegaly were defined as achieving a GH level of less than 1µg/l during OGTT and normal age-related serum IGF1 level.13

**A Stepwise Therapeutic Strategy**

Surgery (usually by the trans-sphenoidal route) is the classic first-line treatment. Tumour excision normalises GH and IGF-1 concentrations in 40–70% of cases,2,14,15 depending on the size of the tumour (microadenomas are more amenable to cure), pre-operative GH concentrations (the success rate is higher when pre-operative GH concentrations are lower) and the experience of the surgeon.

Before the era of medical treatment, radiotherapy was used in second line, when surgery has failed to achieve control of GH/IGF-1 hypersecretion. Fractioned irradiation delivering a total dose of 45–50Gy, yields GH concentrations below 2µg/l and normal IGF-1 levels in 5–60% of patients, after a median follow-up of about seven years.16–18 In studies with longer follow-up, fractionated radiotherapy normalises the IGF-1 level in more than 70% of patients beyond 10 years.17,18 Baseline GH concentration seems to be predictive of treatment outcome. However, radiotherapy leads to variable degrees of hypopituitarism in 80–100% of patients after 10–15 years. Complications such as radionecrosis and optic neuropathy are now rare. In contrast, the risk of stroke may be increased, sometimes many years after irradiation.19 When the lesions are small and located at least 5mm from the optic chiasma, stereotactic irradiation (e.g. using a gamma-knife) is interesting.20–22 According to a recent French study, efficacy seems similar to that of fractionated radiotherapy. Indeed, less than 20% of patients have normal IGF-1 levels and GH <2µg/l, an average of four years after the procedure.23

As surgical treatment, even combined with radiotherapy, is not able to control GH/IGF-1 levels in all patients with acromegaly, a medical alternative is useful in order to achieve the recommended criteria of control of the disease – and to decrease the morbidity – and the mortality associated with acromegaly.

**Medical Treatment**

Three types of drugs are available.

**Dopamine Agonists**

Bromocriptine and other dopamine agonists such...
abergoline are able to improve symptoms of acromegaly in few patients and to decrease GH secretion.

**Somatostatin Analogues**

Somatostatin, the hypothalamic GH-release inhibitory native peptide had too short a half-life to be administered easily. The first synthesised somatostatin analogues (SA), octreotide, is an octapeptide with a prolonged half-life, increased potency and has been available for more than 20 years. Initially given subcutaneously (100–500µg) three times daily, it rapidly proved to be able to control GH hypersecretion in a significant proportion of patients.\(^{24,25}\) A long-acting form (by encapsulation in microspheres) has subsequently been proposed allowing once-monthly intramuscular injections (10, 20 or 30mg) with the same efficacy.\(^{26}\) More than 10 years ago, another SA, named lanreotide (also an octapeptide) was proposed.\(^{27}\) It has also been encapsulated in microspheres allowing a prolonged release for twice or thrice-monthly injections (10, 20 or 30mg) with the same efficacy.\(^{26}\)

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Somatostatin and SAs bind to somatostatin receptors (sst) present on the cell surface of target organs. Five subtypes (1 to 5) have been described. The currently available SAs bind with high affinity to sst2 and 5. As a significant percentage of GH-secreting adenomas seem partially or totally resistant to octreotide or lanreotide, due in part to a variable tumoural expression or reduced receptor density of the five known sst\(^{26}\) there is a place for the development of new SA, more potent and with enhanced binding capacity to some sst. SOM230, a novel analogue displaying high-affinity binding to human sst1, 2, 3 and 5\(^{37}\) is a potent inhibitor of GH and IGF1 in vitro and in several animal models.\(^{38}\) Due to heterogeneous expression of sst2 and 5 in GH-secreting tumours, a bispecific SA, such as BIM-23244 that can activate both receptors could achieve better control of GH hypersecretion in a larger number of acromegalic patients.\(^{39}\) Combination of dopamine agonists and SA may be beneficial for some patients but long-term studies assessing this therapeutic association are not available. Researchers are working on dopastatins that are chimeric drugs able to bind to dopamine and to somatostatin receptors, which may produce a synergistic effect on GH secretion. Side effects of SA are benign: digestive problems are minor and most often transient (abdominal cramps, diarrhoea, flatulence); cholelithiasis occurs in 10–55%, are generally asymptomatic and must be treated conservatively. Despite a reduction in insulin secretion due to SA, glucose tolerance alterations are generally of minor significance.

**Pegvisomant**

This is a recently developed antagonist of GH receptor (GH-R) which blocks the effects of GH at the level of its target organs.\(^{42}\) It was obtained by combining the mutagenesis of the GH gene: a substitution of eight amino acids in the binding site 1 of a molecule of GH, resulting in an increased affinity for the GH-R and a mutation in binding site 2, rendering ineffective the binding to the second molecule of GH-R, and therefore blocking the GH-R dimerization and the intracellular GH signalling. To enhance its half-life, several polyethylene glycol (PEG) molecules were added to the molecule. Pegvisomant has proved to be effective in lowering IGF-I; however, GH concentrations increase and efficacy must only be regarded on IGF-I levels.\(^{43,44}\) The drug is administered once daily, by subcutaneous injection, at a dose of 10, 15 or 20mg. Side effects are limited to hepatitis, justifying follow-up of liver function every month during the first six months.\(^{44,45}\) There is uncertainty about the effects of the drug on tumoural volume, some rare patients displaying a volume increase during treatment with pegvisomant: this may be the consequence of the loose of negative feedback of IGF-I on somatotrophs or, alternatively, to the natural history of the adenoma in some of the patients.

A close surveillance of tumoural volume during treatment with pegvisomant is thus recommended.

**Results of Various Treatments**

- Bromocriptine or other dopaminergic agonists produce cause an improvement in clinical symptoms of acromegaly in half of the patients, while substantially decreasing GH levels in some patients. A review of 31 published studies of bromocriptine involving 549 patients with acromegaly demonstrated very modest results: suppression of GH less than 5µg/l in 20% of cases and normalisation of IGF-I levels in less than 10% of cases.\(^{46}\) Better results seem to be obtained with cabergoline: near 40% of acromegalic patients were reported to have normalised their IGF-I levels in a multicentre study from Belgium.\(^{47}\)

- Treatment with SA has now gained a wide place in the medical treatment of a acromegaly.

**Antisecretory Effects**

GH levels are decreased in 50–80% of patients treated with octreotide subcutaneously three times daily.\(^{48-55}\)
Up to 50% of acromegalic patients may be considered as ‘controlled’ (GH plasma levels less than 2µg/l (20-30%) and/or normal IGF-I (20-60%)) with this treatment.

Similar results are obtained with lanreotide LAR 30mg administered intramuscularly every 10 or 14 days (GH plasma levels less than 2µg/l (30-70%) and/or normal IGF-I (40-70%))27-31,56 or with octreotide LAR given intramuscularly every month at the dose of 10-30mg (GH plasma levels less than 2µg/l (50-60%) and/or normal IGF1 (60-90%)).57-62 Lanreotide Autogel® (60, 90 and 120mg) is at least as effective and well-tolerated as lanreotide PR 30mg injected every 7-14 days.34,35

The various figures obtained between studies are probably explained by the variation in the method used for IGF-I assay, and by the differences in the inclusion criteria chosen in each study. Indeed, in some of the studies, patients were included if they were previously demonstrated to be responsive to octreotide SC, while in others, patients were entered blindly.

Freda et al. performed a meta-analysis on the effects of long-acting SA therapy in acromegaly.63 They found that, among subjects not selected for SA responsiveness before study entry, both GH efficacy criteria and IGF-I normalisation were met in a greater proportion of those treated with octreotide LAR versus lanreotide SR. (54 and 63% versus 48 and 42%, respectively).63

It has long been claimed that the efficacy of octreotide subcutaneously or LAR or lanreotide LP as primary treatment (in de novo patients) was equivalent to that of secondary treatment (in patients previously treated with surgery and/or radiotherapy).55,62,64-66 In fact, according to the meta-analysis of Freda et al., IGF-I normalisation occurred in a greater proportion of secondary octreotide LAR versus primary octreotide-treated subjects.63

Different long-term studies have shown that biochemical cure under long-acting SA seems to improve with time.56,61

**Antitumoural Effect**

Clinically significant tumour shrinkage has been seen in a number of studies, particularly in patients undergoing primary medical therapy whether with octreotide subcutaneously, octreotide LAR or lanreotide SR.67 A meta-analysis of all the published studies involving de novo patients treated with long-acting SA, showed that a ~50% decrease in pituitary mass is achieved.68 Importantly, the initial pre-treatment tumour size is a determinant of the significance of measured shrinkage. Fourteen studies55,62,63,69-78 provided a definition of tumour shrinkage and described the percentage of patients that demonstrated a significant shrinkage in tumour size when used as primary treatment. As a whole, 36.6% of the patients had a significant decrease in tumour size. The mean reduction was 19.4%. The percentage of patients demonstrating tumour size reduction while receiving short-acting octreotide seems to be not different from the percentage of patients receiving long-acting preparations.68

Except for one study,70 persistent tumour growth has generally not been observed in patients receiving SA therapy. When SA are discontinued, tumour regrowth appears to occur within six months.51 In a review of 36 studies involving 921 patients, only three studies reported tumour growth during SA treatment. In these studies, tumour growth was observed either in cases of invasive, resistant tumours,70 in patients treated with lanreotide 30mg after a short-term (one month) treatment,69 or due to the cystic transformation of a tumour.69 Thus, with long-acting treatment, tumour growth is controlled in >97% of patients.67

Pre-operative somatostatin analogue treatment is able to improve the patient’s general condition before pituitary surgery. Some authors also advocate its use for improving surgical remission rates by allowing the tumour to shrink and facilitate a more complete resection. In fact, this question remains controversial: some series have reported a beneficial effect69,70,75,79,80 while others did not.73,81 Nevertheless when an improvement in surgical outcome is noted, it seems to be limited to intrasellar non-invasive macroadenomas.70,79

In patients with large invasive tumours, treated primarily with SA and in whom medical treatment with SA is unable to achieve good GH/IGF-I control, it may be interesting to propose a surgical tumour debulking and to re-introduce SA treatment. This may allow to increase the likelihood of achieving biochemical disease control under SA.82

**Perspectives**

In a recent study, administration of a single dose of 100 and 250µg SOM230 was compared with 100µg octreotide. Some patients showed similar efficacy of both drugs on GH levels, whereas in others SOM230 was either more or less effective, as compared with octreotide. This may be related to its additional suppressive effect on GH secretion via sst5.83 At the present time, there are no human studies with the bispecific SA BIM2344 or with dopastatines.
Treatment with the GH-receptor antagonist pegvisomant, has proved to be effective in the control of clinical symptoms of acromegaly and allows normalisation of IGF-I levels in the great majority of patients.43,44 In a randomised double-blind placebo controlled trial during 12 weeks, in 112 patients, at a dose of 10, 15, 20mg/d, normal IGF1 levels were achieved in 89% of patients with high dose of pegvisomant (20mg/d subcutaneously).43 In a study collecting all the data obtained with this drug, normalisation of serum IGF1 levels was observed in 97% of 90 patients for more than 12 months, using doses of up to 40mg.44 While treatment with SA may be responsible for a worsening of glucose tolerance (due to its suppressive effects on insulin secretion), pegvisomant, by acting only on insulin resistance – which is improved in parallel with the reduction of IGF-I levels – and not on insulin secretion does not impair glucose tolerance, and may thus be recommended in acromegalic patients with diabetes or IGT.84-86 Van der Lely et al. reported no significant alteration in mean tumour volume. However, tumour growth was observed in few patients.44 Interestingly, in one of them cotreatment with octreotide halted further tumour growth and induced a synergic decrease in serum IGF1 concentration.85 Recently, an association of SA (octreotide LAR once monthly) and pegvisomant (administered weekly at a dose of 60mg on average) was shown to normalise IGF-I in 18 of 19 (95%) patients whose acromegaly was resistant to SA administered alone.86 This combined treatment is effective, might increase compliance, and could greatly reduce the costs of medical treatment for acromegaly in some patients.

TREATMENT OF ACRHOMEGLY

The proposed management of patients with acromegaly (that largely corresponds to the recommendations of a recent consensus meeting on medical treatment of acromegaly89) is shown in Figure 1.

1. Trans-sphenoidal surgery is generally the first-line therapy. In selected patients, either if surgery is contraindicated (e.g. compromised cardiac or respiratory function) or if the probability of surgical cure is low (e.g. in patients with very large and/or invasive tumours), SA may be a reasonable primary therapeutic modality provided that the tumour does not threaten vision or neurological function.

2. After surgery a biochemical evaluation (GH and IGF-I) allows to know if the disease is controlled or not. In case of persisting disease, SA are generally prescribed as a second-line treatment (eventually preceded by a trial of dopamine agonists, particularly cabergoline).

3. If the disease is controlled under SA, regular assessment (both biochemical and on tumoural volume) is necessary.

4. In case of persistent disease despite SA treatment, some patients may be reoperated, in particular for debulking a residual tumour before a novel trial of SA treatment. Otherwise, there is an indication for third-line treatment which may be either radiotherapy or GH antagonist (pegvisomant).

   a. Post-operative radiation therapy (50 to 55Gy) is performed for partially resected tumours or when GH levels remain elevated. SA are generally given in waiting for the delayed effects of radiation therapy.

   b. However, due to the potential side effects of radiotherapy, we generally prefer to delay radiation therapy and to first switch patients from SA therapy to pegvisomant if there is no concern with tumour mass. If there is a concern with tumour mass, pegvisomant may be associated with SA.

5. During treatment with pegvisomant, close monitoring of IGF-I (for evaluating acromegaly control) and tumour mass is recommended, to diagnose a potential increase in tumour volume which may necessitate surgery and/or radiotherapy.
multicenter trial in 103 patients—a clinical research center study (published erratum appears in J Clin Endocrinol Metab (1995);80(11): p. 3,238), J Clin Endocrinol Metab (1995);80(9): pp. 2,768–2,775.


Barkan A L, Lloyd R V, Chandler W F, et al., Preoperative treatment of acromegaly with long-acting somatostatin analog...
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