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Medical therapy in acromegaly

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Introduction Acromegaly is a serious endocrinopathy that is associated with considerable morbidity and increased mortality (1–3). Although the pituitary tumours associated with acromegaly are usually benign, the elevated levels of growth hormone (GH) and insulin-like growth factor (IGF)-1 lead to a wide range of cardiovascular, respiratory, endocrine and metabolic alterations. Thus, number of co-morbidities are present in patients with acromegaly, including arthropathy, hypertension, sleep apnoea, diabetes, dyslipidaemia, cardiomyopathy, colon polyps, goitre, and headache (4–7).In a recent meta-analysis, the weighted mean of the standardized mortality ratio (SMR) from 16 published studies of patients with acromegaly was 1.72 (8). In the more recent studies improved survival is reported, presumably due to modern treatment modalities and strictly defined cure criteria, but nevertheless there was a 32% increased risk for all-cause mortality acromegaly (8). Patients with random serum GH levels < 2.5 ng/ml after treatment, mostly measured by standard radio-immuno assay (RIA), had mortality close to expected levels (SMR 1.1) compared with a SMR of 1.9 for those with a level > 2.5 ng/ml. Similarly, a normal serum IGF-1 level for age and sex was associated with a SMR of 1.1 compared with a SMR of 2.5 for those with elevated IGF-1 levels (9).

Treatment goals and approaches Currently, treatment options in acromegaly include surgical removal of the tumour, medical therapy, and radiation therapy of the pituitary. Each treatment modality has specific advantages and disadvantages but the optimal use of these treatments and their combination should result in a reduction of mortality in the acromegaly patient population to that of general population.

Goals of treatment are to:

- Inhibit GH hypersecretion and normalize IGF-1 levels;
- Control tumour growth and relieve the pressure that the growing pituitary tumour may be exerting on the surrounding brain areas;
- Preserve normal pituitary function or treat hormone deficiencies;
- Improve the symptoms of acromegaly.

Based on the fact that basal GH levels > 2.5 ng/ml (3, 10), elevated IGF-1 (3, 11, 12), age and disease duration (3, 12), hypertension (3) diabetes and cardiac diseases are the main determinants of mortality, biochemical goals to control mortality are a GH< 2.5 ng/ml or a normal range and sex adjusted IGF-1 levels. Measurement of GH during an oral glucose tolerance test (OGTT) may be preferred to a random GH measurement, and a biochemical control is defined as a nadir of GH < 1.0 ng/ml during the OGTT. Successful treatment of GH/IGF-1 hypersecretion is expected to improve co-morbidities in patients with acromegaly to varying degrees. Nevertheless, some may persist even after successful control of acromegaly, and some may improve even if control is not achieved (13). So, all co-morbidities should be actively diagnosed and treated irrespective of GH and IGF-1 levels, and therapeutic decisions should be made according to both clinical and biochemical assessment.

Medical therapy Currently, there are three drug classes available for the treatment of acromegaly: dopamine agonists (DAs), somatostatin analogues or somatostatin receptor ligands (SRLs), and a GH receptor antagonist (GHRA). After transsphenoidal surgery, SRLs are generally the first line of treatment, followed by GHRA or DAs.

Somatostatin receptor ligands The SRLs act primarily via somatostatin receptor subtypes 2 and 5 leading to a decrease in adenoma GH secretion. They have a multitude of other endocrine and non-

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endocrine effects, including inhibition of glucagon, VIP, and gastrointestinal peptides. Periodically GH/IGF-I levels should be monitored to assess response. The use of SRLs is most appropriate (14):

- After surgery has failed to achieve biochemical control;
- To provide disease control, or partial control, in the time between administration of radiation therapy and the onset of maximum benefit attained from radiation therapy;
- As first-line therapy when there is a low probability of a surgical cure (for example, large extrasellar tumours with no evidence of central compressive effects);
- Before surgery to improve severe co-morbidities that prevent or could complicate immediate surgery (15).

Long-term studies indicate that approximately 70% of patients receiving SRLs have GH levels < 2.5 ng/ml and normalized IGF-1 and maximal benefit may be achieved after 10 years of therapy (16). However, these studies often include patients pre-selected for GH responsivity. In unselected populations, SRLs reduce GH to < 2.5 ng/ml and normalize IGF-1 in 44% and 34% of patients, respectively (17). Tumour shrinkage of > 20% occurs in approximately 75% of acromegaly patients receiving these drugs (mean 50% reduction in tumour volume) (18). These peptide analogues have a proven safety record. Common side effects include altered gastrointestinal motility with a reduction over the first few months of treatment. Multiple small gallstones and gallbladder sludge commonly occur, but rarely cause cholecystitis. Because of alteration in counter regulatory hormones (eg, insulin, glucagon, GH), hypoglycaemia or hyperglycaemia can occur. Bradycardia, cardiac conduction abnormalities, and arrhythmias have been reported. Thus, patients on insulin, oral hypoglycaemias, beta-blockers, and calcium channel blockers may need dosage adjustments. Secondary hypothyroidism can also occur because of parallel inhibition of thyrotropin secretion. Patients should remain on the same dose for 3 months (assuming medication tolerance) to properly assess adequacy of treatment and the need for dose titration. In well-designed trials, the long-acting formulations appear to be equivalent in the control of symptoms and biochemical markers in patients with acromegaly (19).Octreotide (Sandostatin) - adult dose: initial: 50 μg SC tid; can increase to 500 μg tid; doses of 300–600 μg/d or higher seldom result in additional benefit. Adverse effects include nausea, abdominal pain, diarrhoea, and increased incidence of gallstones and biliary sludge. Caution is needed in renal impairment. It is usually safe in pregnancy but benefits must outweigh the risks (category B).

Octreotide LAR (Sandostatin LAR) The long-acting somatostatin analogue is administered every 4 weeks (adult dose 10–30 mg i.m. q28 days). Similar improvements occur in GH/IGF-I levels compared to octreotide but are associated with fewer adverse effects. Safety for use during pregnancy has not been established (category C).

Lanreotide (Somatuline Depot) This octapeptide analogue of natural somatostatin elicits high affinity for human somatostatin receptors 2, 3, and 5. Inhibits a variety of endocrine, neuroendocrine, exocrine, and paracrine functions, including basal secretion of motilin, gastric inhibitory peptide, and pancreatic polypeptide. Markedly inhibits meal-induced increases in superior mesenteric artery blood flow and portal venous blood flow. Also significantly decreases prostaglandin E1-stimulated jejunal secretion of water, sodium, potassium, and chloride. Reduces prolactin levels in acromegalic patients, when treated long term. Fatal risk is revealed in studies in animals but is not established or not studied in humans (category C in pregnancy). Lanreotide is indicated for long-term treatment of acromegaly in patients who experience inadequate response to other therapies. Adult dose–90 mg s.c. q 4 week for 3 months initially; dosage range 60–120 mg q4 week. In moderate to severe renal or hepatic impairment: 60 mg s.c. q 4 week for 3 months. The dose is adjusted according to GH/IGF-1.

Dopamine agonists DAs are the only oral medication available for acromegaly. These agents are usually added to SRLs if complete remission has not been achieved. They have modest effects if used as a single agent and are less potent than SRLs in decreasing both GH (42.4% *vs.* 62.8%, $P < 0.008$) and IGF-1 (8% *vs.* 40.4%, $p = 0.05$) (21). Clinical situations where DAs may be useful include (14):

- Preferred oral medication;

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- After surgery (very occasionally as first-line therapy) in selected patients, such as those with markedly elevated prolactin and/or modestly elevated GH and IGF-1 levels;

- As additive therapy to SRLs in patients partially responsive to a maximum SRLs dose - about 50% of such patients may achieve control of GH and IGF-1 with combination therapy (20).

Bromocriptine (Parlodel) Acts on central dopamine receptors. It is considered to be more effective in tumours that co-secrete prolactin and the dose used to treat acromegaly is usually much higher than that used for hyperprolactinemia. Initial adult dose is 1.25 mg p.o. and is increased gradually; maintenance dose is 20–30 mg p.o. adverse effects include nausea, vomiting, headaches, nasal congestion, orthostatic hypotension, and digital vasospasm. Patients tend to develop tolerance to adverse effects. Caution is needed in renal or hepatic disease. Bromocriptine is usually safe in pregnancy but benefits must outweigh the risks (category B).

Cabergoline (Dostinex) Of the two DAs, the long acting one - Cabergoline is considered to be more effective in acromegaly, and this is limited - monotherapy is effective in less than 10% of patients (22). The weekly dose is 1.0–2.0 mg. High doses of Cabergoline in patients with Parkinson's disease (higher than doses used in acromegaly), and a prolonged duration of therapy, are associated with the development of cardiac valvular abnormalities. Valvular disease has not been found in patients receiving the conventional doses used for pituitary tumours (23). Patients receiving higher than conventional doses of Cabergoline for prolonged periods of time should be monitored by performing echocardiography.

Growth hormone receptor antagonist Pegvisomant (Somavert) is a recombinant DNA analogue of GH that is structurally altered to act as a GHRA. It selectively binds to GH receptors on cell surfaces, thereby blocking endogenous GH binding. This action interferes with GH signal transduction, resulting in decreased IGF-I, IGF binding protein-3 (IGFBP-3), and acid-labile subunit. The indications for its use are (14):

- In patients that have persistently elevated IGF-1 levels despite maximal therapy with other treatment modalities.

- Possibly as monotherapy or in combination with a SRLs in other patients.

Pegvisomant is highly effective in acromegaly and significantly improves the quality of life in patients that require both SRLs and pegvisomant to achieve biochemical control (24). Loading adult dose is 40 mg s.c., and maintenance dose is 10 mg s.c qd initially. It may increase or decrease q 4-6 week by 5 mg increments as determined by IGF-I levels. The dose may not exceed 30 mg/d. Safety issues with GHRA include liver function abnormalities and tumour growth. Tumour growth is infrequent (<2%) (25) and approximately 25% of patients have liver function abnormalities, but these appear to be transient in most patients without changing the GHRA dose (26). Whether the tumour growth is due to the GHRA or merely reflects ongoing tumour growth when there is no therapy directed specifically at the tumour has not been established definitively. Pegvisomant improves insulin sensitivity without affecting insulin secretion and may increase insulin or oral hypoglycemic effect. Pegvisomant treatment decreased fasting insulin, fasting glucose and HbA1C and improved metabolic control in acromegalic patients with and without diabetes (26). Recent publications suggest that GHRA may be useful in combination therapy with a SRL (27, 28), but there are no direct comparisons between combination therapy and monotherapy with GHRA. The combination of a SRL and a GHRA may be useful for acromegaly that is resistant to other treatment modalities, for patients who have not achieved biochemical control after surgery, or to improve cost-effectiveness in patients that would otherwise require high-dose GHRA monotherapy.

Conclusion No single treatment is effective for all patients. Treatment should be individualized, and often combined, depending on patient characteristics such as age, duration of the disease, tumour size, complications and co-morbidities. There are certain areas where more data are needed on the use of medical therapies. No head-to-head studies of the different SRLs of adequate design and power are available to recommend one drug over the other. More data on the potential use of GHRA as a first-line treatment or in combination with SRLs are needed. The relative cost-effectiveness of all medical therapies as monotherapy, or in the various combination options, requires evaluation. In addition to medical therapy for GH/IGF-1 hypersecretion, treatment of co-morbidities has an important impact on quality of life and mortality.

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