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Medical Therapy of Acromegaly

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Acromegaly is a chronic disorder associated with increased mortality and morbidity. There are several studies have shown that mortality rate of acromegalic patients become similar to normal population when normal GH values are achieved. Surgery is the first line treatment of acromegaly. But the remission rates with surgery alone are low. Therefore, it is necessary to add other treatment modalities. Such as somatostatin anlogs, dopamin agonists, GH receptor antagonists and radiotherapy.

Keywords: Acromegaly, treatment

Acromegaly, is a chronic disorder associated with increased mortality if it's not treated (1). Malignancies, cardiovascular and pulmonary complications are the most common causes of mortality (2,3). In acromegaly, the therapeutic goal is to restore normal growth hormone secratory dynamics, normalize serum insulin like growth factor (IGF-1) and shrink the pituitary mass, while maintaining the normal anterior and posterior pituitary functions. Normalizing GH and IGF-1 levels will result with reduction in the complications that influence life quality and will reduce the pathologies that increase the vascular damage, such as diabetes mellitus, insulin resistance, lipid abnormalities and cardiomyopathies. Surgery, radiotherapy and medical therapy are current treatment options to achieve these goals. None of these therapies are satisfactory alone and mostly it is necessary to add different treatment modalities together.

Several studies have shown that the mortality rate of acromegalic patients is similar to that of the general population when normal growth hormone levels are achieved (4). Various targets for treatment have been used in the past but the current consensus criterias are; to aim for a basal GH level below 2.5ng/ml, nadir GH levels less than 1ng/ml after an oral glucose tolerance test and a normal IGF-1 level for age and gender (5). In the post operative course some patients have normal IGF-1 but abnormal GH responses. These patients require closer follow-up to document potential disease recurrence.

Surgery is the first line treatment for most patients with acromegaly. Surgery alone provides 70-80% remission in microadenomas and less than 50% remission in macroadenomas (6). Therefore many patients who undergo initial surgery require additional therapy.

Recently, considerable developments occurred in medical treatment options in acromegaly. Medical therapies such as long acting somatostatin analogues, dopamine agonists and a new class of agents known as GH receptor agonists are new options for the persisting disease. Moreover, medical therapies become a first line therapy for some selected patients.

Somatostatin Analogues

Growth hormone secreting adenomas express somatostatin receptor subtype 2 and 5. This form the basis for using octreotide and lenreotide, which are long acting somatostatin analogues and bind with affinity to these 2 subtypes of receptor.

Octreotide is a synthetic somatostatin analog, which was first used to treat acromegaly in 1980s. Octreotide has a prolonged half life (subcutaneously 80-100 minutes versus endogen somatostatin 1-3 minutes) and inhibits GH secretion with a potency of 45 times greater then endogen somatostatin. The rebound GH secretion does not occur after octreotide injection. Recommended

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daily octreotide doses are 50-500 µg/day given in a subcutaneous injection three times a day. Several studies have shown that octreotide reduces GH concentrations below to 2.5 ng/ml in 22% to 45% of patients following 6 months of therapy (7,8). After it was shown that continuous infusions was more effective and was associated with fewer adverse effects and less compliance of subcutaneous injections, prompted the development of long-acting formulations of somatostatin analogues. Octreotide LAR is usually administered deep intramuscularly every 28 days while Lanreotide LAR is administered intramuscularly every 7-14 days. Lanreotide autogel is given deep subcutaneously every 28 days. The first studies of these analogues were published in 1997. Flogstad et al. have evaluated the long term effects and safety of 20-40 mg Octreotide LAR, in 14 acromegalic patients. They showed that 9 of 14 patients achieved GH values less than 2.5 ng/ml. Most effective dose was 30 mg (9). In the same year Caron et al. published the data of 3 year follow-up with treatment of Lanreotide- LAR. They have report that, mean GH values were 2.5 ng/ml or less in 27% of patients and the normal IGF-I concentrations were achieved in 63% of patients (10). In 1998, Davies et al. reported that three years octreotide LAR treatment lowers GH values less than 2.5ng/ml in 50% of patients and these results remain unchanged during 3 years (11). Numerous studies have been conducted regarding the efficacy of this therapy. Verhelst et al. followed 66 acromegalic patients with 30 mg lanreotide LAR in every 7-14 day and showed 44% IGF-1 normalization and 45% achievement of GH values less than 2.5ng/ml (12). Colao et al. treated 36 active acromegaly patients with sandostatin LAR and they achieve normal IGF-1 in 61.1% and GH less than 2.5ng/ml in 69.4% during 12-24 month follow-up (13). Cozzi et al. evaluated of a four year treament with octreotide LAR retrospectively in 110 patients with acromegaly. They observed IGF-1 normalisation in 75% of patients. GH fell less then 2,5 mg/l in 72% and less then 1 mg/l in 27%patients in their study (14). Freda et al. published a metaanalysis of 44 trials, included more then 3 months of secondary octreotide LAR or lanreotide SR therapy or of primary octreotide LAR, lanreotide SR, or sc. octreotide therapy, and clearly reported data on biochemical efficacy and/or tumor shrinkage. They have shown that the efficacy of octreotide LAR is greater than lanreotide SR among subjects unselected for prior somatostatin analog respponsiveness. Preselection is a significant positive predictor of IGF-1 normalisation and is associated with increased odds of tumor shrinkage, which is also greatest with octreotide LAR. Biochemical efficacy is similar, but tumor shrinkage is greater when these drugs are given as primary vs. secondary therapy (15). In our clinic thirty three patients (26 female and 7 male, mean age; 43,94±14.01 SD years) with active acromegaly despite earlier surgery and/or radiotherapy was follow-up for 40 month and all patients started with 28 day interval administration of 20 mg S-LAR by intramuscular administration for three months thereafter, the S-LAR dose had been individually tailored with the aim to achieve normal age adjusted level of IGF-1 and suppression of nadir GH levels in OGTT less than 1 ng/ml (unpublished data). Results are summarized at table 1.

Somatostatin analogues are very effective in improvement of the symptoms. Over 75% of patients experienced improved general wellbeing, and soft tissue swelling, head ache, perspiration dissipates during the 6 month of therapy (16). Cardiovascular functions resolves and hyperglycemia and sleep apnea improves. Boysan SN et al. showed that two years of octreotide LAR led to decrease in intima-media thickness (IMT) of

Table 1. Sandostatin LAR effect on GH and IGF-1

	initial	6th month	12th month	30th month	40th month
MinGH values in OGTT	2.71	1.6[a]	0.31[b]	1.5[c]	0.89[d]
(ng/ml)	(1.35-6.9)	(0.36-4.10)	(0.18-0.65)	(0.83-4)	(0.58-1.35)
IGF-1	530	340[e]	400[f]	396[g]	482[h]
(µg/l)	(420-600)	(230-460)	(224.4-600)	(318-468)	(308-580)

Results were defined as median and interquartile ranges

a, p=0.03; b, p=0.00; c, p=0.39; d, p=0.00; e, p=0.01; f, p=0.48; g, p=0.49; h, p=0.47

carotid artery, which is a good indicator of premature atherosclerosis (unpublished data).

Tumor shrinkage effect of somatostatin analogues are less pronounced than dopamine agonists treatment of prolactinomas, considerable tumor reduction (reduction of its initial length at 20 to 50%) is ensured averagely at 30% of patients. Tumor shrinkage and biochemical control are not always correlated and maximum tumor reduction occurs in the first year of the therapy (17). To date there is no evidence that tumor shrinkage improves the remission rate, that's why, the first goal of treatment remains biochemical control. In our series with 33 acromagalic patients tumor volumes was reduced from 1.18 cm to 0.21 (p=0.083).

The long acting somatostatin analogues therapy prior to surgery is still controversial. Some authors indicate that preoperative use of octreotide induce shrinkage of the tumor and improves the postoperative remission rate (18). However, this effect was not confirmed by other studies (19). Moreover, it was shown that preoperative octreotide for 3-6 months demonstrated improved postoperative biochemical control and reduced hospital length of stay (20).

In order to investigate the effect of necrosis and apoptosis in long acting octreotide in tumor, S-LAR is performed on randomly chosen 8 patients out of 15 who have been observed and treated in our clinic, before the surgery (median using period: 120 days [IQR:16.25-450.00]. No treatment is carried out on the remaining 7 patients. Fas-expression, which is an indicator of apoptosis, is investigated through immunohistochemical staining of CD 95 (fas)ab-3. At the end, it is observed that S-LAR does not increase necrosis in tumor; however it significantly increases apoptosis (21).

Somatostatin analogues are generally well tolerated. The most common adverse effect is gastrointestinal (abdominal cramps, diarrhea and fatty stools). These are usually mild and transient. In contrast, the effects on the composition of bile and gallbladder contractility last longer. These drugs attenuates gallbladder contractility, delays emptying, and leads to reversible sludge formation and asymptomatic cholelithiasis in up to 20% especially with short acting forms. The formation of cholelithiasis and bile sludge are less frequently observed in long acting forms, 6.3% and 4.7% respectively (22). However, routine ultrasound examinations are not recommended for these patients (17). Fat malabsorbsion, transient hair loss, pain in place of injection and vitamin B12 deficiency have rarely been reported.

In conclusion, the treatment with somatostatin analogues has been widely shown to act rapidly and to reduce GH hypersecretion and to decrease IGF-1 concentrations effectively. The recent availability of somatostatin analogues provided in slow release formulation such as S-LAR, has further improved patients' compliance to long term treatment. However, their high cost of production and inefficacy to provide control on %36-52 patients constitute the weak sides of these medicines.

Dopamine Agonists

Dopamine, D2 receptor agonists, bromocriptine and long acting dopamine agonist cabergoline, have been used to suppress GH secretion in acromegaly. In healthy adults, dopamine agonists increase GH secretion, in patients with acromegaly, dopamine agonists paradoxically decrease GH secretions. It was reported that bromocriptine normalize GH in 20% of patients and IGF-1 in only 10% of cases (23,24). In a large metaanalysis of 28 studies including a total of 500 patients were evaluated and it was found that bromocriptine reduces GH less than 10ng/ml in 50%, less than 5 mg/ml in 10-20%, and improves symptoms in 70% of patients. However, tumor reduction observed in only 10% of patients (25,26). Although reports that implicated the advantages of high doses up to 60 mg/day, it is widely accepted that 20 mg/day is the optimal dose (27,28). At higher doses side effects are more prominent. The principal side effects of dopamine agonists are nausea, vomiting, abdominal pain, orthostatic hypotension, nasal congestion and cold induced vasospasm. These adverse effects may disappear during long term therapy, especially if the dose is titrated very gradually.

Cabergoline, a long acting and more potent dopamine agonist, is better tolerated when compared to bromocriptine. It has a half life of approximately 65 hours and duration of action ranging from 7 to 14 days when given orally. It is generally admi-

nistered once or twice a week. The recommended doses vary between 0.5 mg/ week and 0.5 mg/day.

Dopamine agonists are effective especially in patients with GH/PRL co-secreting adenoma and in patients with D2 receptor expressing adenoma. The combined use of octreotide and dopamine agonists may be useful in patients partially resistant to somatostatin analogues.

GH Receptor Antagonist: Pegvisomant

Pegvisomant, genetically engineered analogue of human growth hormone, functions as growth hormone receptor agonists. GH action through the surface membrane is mediated by ligand induced GH receptor dimerization. Pegvisomant, increase its affinity for one of the binding sites on the receptor and abolish binding to a second site, thereby prevents functional physiological dimerization of the receptor. Pegylation, that is addition of polyethylen glycole molecule residues to the molecule, increase the circulating half life and reduce the immunogenity (29). Pegvisomant is a higly selective ligand for the growth hormone receptor and it does not cross-react with other receptors. Pegvisomant is unique among treatments for acromegaly as its efficacy is independent of tumor characteristics and it does not lower circulating GH levels. Since GH levels do not fall with treatment, GH levels cannot be used as a measure of disease activity, hence the primary goal of therapy is to lower serum IGF-1 to age and gender related reference range.

The first published study of pegvisomant was a multi centre trial in which 112 patients with active acromegaly were randomized to placebo or one of three doses of pegvisomant (10,15 or 20 mg) daily for 12 weeks. There was a significant dose dependent reduction in serum IGF-1 levels with normalization of IGF-1 in 89% of patients receiving the 20 mg/day dose (30). A subsequent study included 160 patients treated with pegvisomant for an average of 18 months. By using daily doses up to 40 mg serum IGF-1 concentrations normalized in 97% of patients with high tolerability and without evidence of tachyphylaxis (31). Tumor shrinkage is not an expected effect of pegvisomant therapy. It has been suggested that the marked reduction in IGF-1 seen during pegvisomant therapy could remove feedback inhibition of pituitary GH secretion and induce tumor growth which thought to be a potential complication. Average tumor volume increase was not reported in previously mentioned studies. However, 59% of patients had undergone a previous radiotherapy and it may influence the results. It was also reported 2 cases of significant increase in adenoma sizes. None of the patient with tumor enlargement had undergone previous radiotherapy.

Caloa et al. examined efficacy of 12 month treatment with GH receptor antagonist pegvisomant in 16 patients with acromegaly, resistant to long term high dose somatostatin analog treatment. They use pegvisomant at doses of 10-40 mg sc. daily. They observed IGF-1 normalisation in 57% of patients after 6 months. They observed tumor volume growth in 2 patient, but the mean tumor volume remained stable during study (32).

Dual blockage of GH axis with pegvisomant and somatostatin analog could also be feasible in resistant acromegalic patients. Jorhensen et al. studied cotreatment of acromegaly with a somatostatin analog and pegvisomant in 11 patients. They observed lowest IGF-1 levels with cotreatment. Pegvisomant increased endogenous GH levels, but it was countered by somatostatin analog cotreatment (33).

The greatest clinical advantage of pegvisomant is its effect on glucose and on insulin sensitivity. It is able to reduce both insulin and glucose concentrations improving much more insulin sensitivity and glucose tolerance when compared with somatostatin analogues (34). Pegvisomant is well tolerated, with few adverse effect reported. The principal side effect described to date has been transient elevation of hepatic transaminases in two patients (17).

Consequently, pegvisomant is the most effective drug that reduces IGF-1 among existing therapies. Since all mortality datas are based on GH levels, clinical significance of IGF-1 reduction has not been clearly defined yet. In two cases of acromegalic patients, without previous radiotherapy, enlargement in adenoma were reported. In conclusion, especially without previous radiotherapy, all patients should be observed closely for tumor enlargement and all patients must be followed carefully for liver dysfunction.

Other Medical Treatment Options

In 1980's it has been shown that estrogen reduced IGF-1 although it is not possible to use on male patients, it can be added to other medical therapy methods in female patients (35). In recently published datas, it is stated that selective estrogen modulators such as tamoxifen and raloxifen have similar effects to estrogen in acromegaly, and can be used in selective group of patients (29).

SOM 230 is a new somatostatin analogue that is currently being investigated for the treatment of acromegaly. However, clinical trials have not been completed, that's why it is still unclear that it will be more effective than Sandostatin LAR or lanreotide. But its phase I and phase II studies are very encouraging and it is under extensive study (36).

It is also interesting the recent observation that somatostatin receptors undergo, besides homo-, hetero-, oligomerization and may form heterodimers with D2 dopamine receptors, resulting in receptor complexes with modified functional properties. These findings have prompted to chimeric compounds that interact with SST2, SST5, and D2. Moreover, it was shown that these compounds have additive effect to suppress GH and PRL levels when compared to use the drugs alone (36).

Use of Medical Therapy as First Line Treatment and Acromegaly Treatment Algorithm

Although, surgery by an experienced operator may provide cure for long term, patients with macroadenoma and invasive adenoma have still unacceptably high postoperative GH and IGF-1 levels. Somatostatin analogues are often used prior to surgery or as an adjunctive treatment following radiotherapy. There were no significant differences

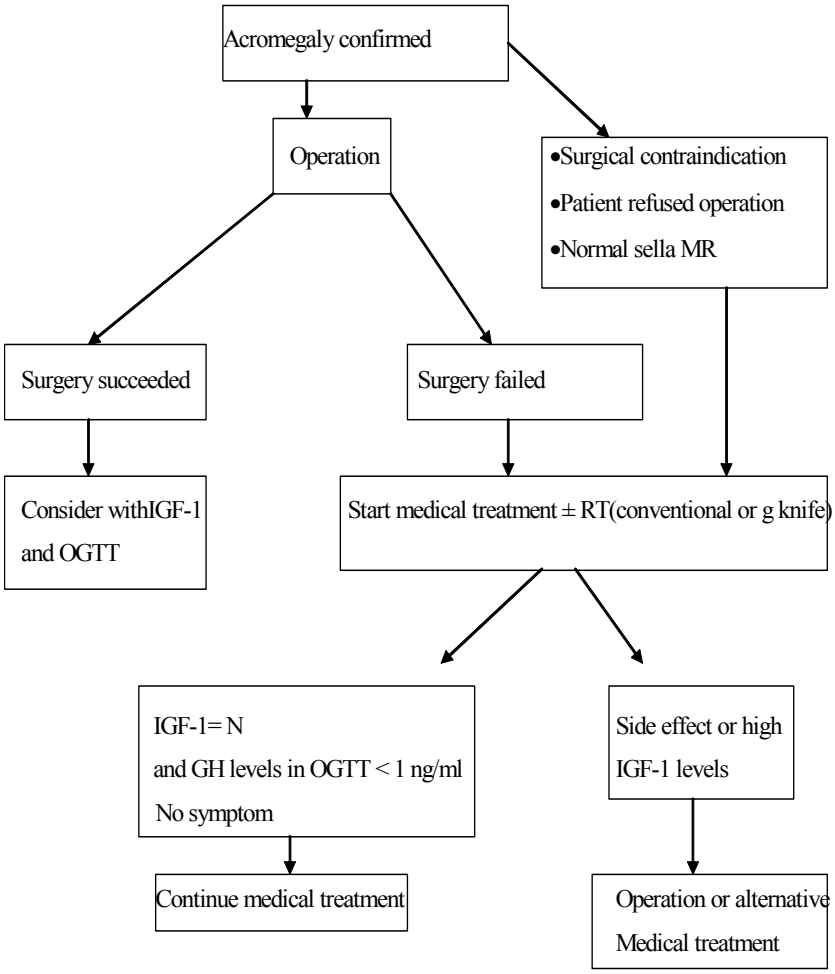

Figure 1. Acromegaly treatment algorhytm

Adopted from Clemmons et al. J Endocrinol Metab 2003;88:4759-4767

in outcome between primary and adjuvant somatostatin analogue treatment. Their use as a primary treatment modality however, has been supported by recent studies. Bevan et al. treated 27 denovo acromegaly patients with octreotide and observed 79% of patients achieved GH levels below 2.5 mg/l and 53% normal IGF-1 (37). Caloa et al. treated 15 acromegalic patients with octreotide for 12-24 weeks and observed GH levels below 2.5 mg/l in 73% of patients and normal IGF-1 levels in 53% of patients (13).

Since first line somatostatin analogue therapy is attractive for patients with poor surgical outcome, such as patients with large adenoma, the impact of these drugs on the tumor mass is of paramount off importance and has to be evaluated. It was shown that somatostatin analogues are induce tumor shrinkage in about 2/3 patients and it is more prominent in patients without previous treatment (37).

Primary medical therapy is being increasingly advocated in patients unlikely to be cured in surgery, such as invasive adenomas, patients unwilling to go surgery and patients with contraindication to surgery. Cost of somatostatin analogues are of the up most importance if medical therapy is to be continued long term.

Treatment algorithm has shown in figure 1.

Radiotherapy

Conventional radiotherapy

Pituitary radiotherapy has been used for many years in acromegaly. Radiotherapy is administered a total dose of 4500 to 5000 rad. Tumor growth is prevented after radiotherapy. However after conventional radiotherapy GH and IGF-1 decline slowly and many years are necessary to obtain biochemical normalisation (up to 20-25 years). GH levels declined in 70-90% of patients when cure was defined as GH less then 5ng/ml. However using existing criteria for the cure of acromegaly has demonstrated that radiotherapy is much less effective than previously thought. IGF-1 normalization is less consistent being reported to normal only in 1/3 of patients. As hypopituitarism is a common side effect (around 60-70%) and as concerns remain over the risk of second tumor formation (about 2% after 20 years) after radiotherapy, and for possible late complications such as damage to the optic nerve and chiasm, seizures and radionecrosis of brain tissue, this modality is not recommended in treatment of acromegaly (38).

Gamma knife radiosurgery

Gamma knife radiosurgery is a modern form of radiotherapy. It is delivered a single session from a cobalt 60 source by focused radiation with little radiation to the surrounding brain tissue. With increase precision and accuracy, further enhanced by the use of MRI for radiological localization of the lesions, a high dose of radiation can be delivered in a single session while minimizing the risk of serious complications. It is especially useful for recurrent tumors or remnants of tumor that are at least 5 mm away from the optic chiasm. In a rewiev of 11 studies of a total of 256 patients it was showed that 35% of patients achieved normalized IGF-1, which is identical of con-ventional radiotherapy. With gamma knife radio-therapy hormonal hypersecretion control begins earlier (about 1.4 years). Side effects of gamma knife are similar to conventional radiotherapy but occur less frequently. Hypopituitarism occurs in 29% patients (38). However, long term studies are needed to determine the safety and efficacy of gamma knife surgery.

In conclusion, morbidity and excess mortality can be reversed by optimal treatment to achieve normal GH, IGF-1 levels and reduced tumor size. To achieve these objectives multimodal treatment is required.

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