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Treatment of Acromegaly

Future

Ines Donangelo and Shlomo Melmed

Cedars-Sinai Research Institute, UCLA David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California

Recent progress in the therapy of GH-secreting pituitary tumors includes three treatment modalities: surgery, radiotherapy, and medications. A combination of treatment options is often required to attain therapeutic goals, increasing the potential for a combination of unwanted side effects. The focus of this review is to discuss medical therapy of GH-secreting adenomas focusing on newer drug compounds. In selected cases, therapeutic goals are attained with somatostatin analog treatment alone. The GH receptor antagonist controls IGF-I hypersecretion, and its use in combination with somatostatin analogs in selected patients is tempting but requires further evaluation. Somatostatin multireceptor ligand SOM230 and a somatostatin–dopamine chimeric ligand are new compounds that may improve therapy outcome. Careful individualization of therapy is important in deciding the ideal treatment approach, and primary medical therapy may be recommended in selected patients.

Key Words: Acromegaly; pituitary adenoma; somatostatin analog; GH receptor antagonist; dopamine agonist; medical therapy.

Introduction

Goals of pituitary tumor treatment include normalization of excessive hormonal secretion and alleviation of pituitary mass effects, while preserving endogenous pituitary function. Moreover, ideal therapy should prevent tumor recurrence, and should not cause additional harm to the patient. Therapeutic options for the treatment of pituitary tumors include surgery, radiotherapy, and medications. Not infrequently, combination of more than one treatment option is necessary to attain normal hormone levels and/or for improvement of tumor mass effect, leading to the potential for a combination of unwanted side effects. Progress in the therapy of pituitary tumors over the last few years includes improved surgical technique and application of novel technology (e.g., endoscope and neuronavigation-assisted technique), which have led to increased totally resected tumor rates *(1)*. Radiosurgery for the treatment of pituitary adenomas has the advantage of reducing the risk of central nervous system damage caused by conventional radiotherapy and is associated with high tumor control rate *(2–5)*. Studies on novel drugs that decrease pituitary hormone hypersecretion and/or that lead to tumor shrinkage are also being reported.

Dopamine agonists are the initial treatment choice for prolactinomas as they usually lead to significant decrease in tumor size and reversal of clinical abnormalities associated with high serum prolactin levels *(6,7)*. Surgery is the only viable therapeutic option for clinically non-functioning adenomas and is the mainstay of treatment for Cushing's disease. Primary medical therapy should not be considered for these pituitary tumor subtypes because currently available drugs do not decrease tumor size or normalize serum pituitary hormone levels *(8)*. Treatment of acromegaly differs from the other pituitary tumor subtypes in that the ideal therapeutic approach should be individualized. Transsphenoidal surgery is considered the initial treatment because it potentially leads to GH and insulin growth factor-I (IGF-I) normalization and reversal of tumor mass effects. However, 70% of GH-secreting tumors are large and often invasive macroadenomas, and in these cases patients are infrequently cured by surgery, and require medical treatment. Several drugs, particularly somatostatin analogs, control hormone excess and contribute to decreased adenoma size *(9–12)*. Primary medical treatment can also be considered in some selected patients with acromegaly. A review on medical therapy of GH-secreting adenomas is addressed below, focusing on the newer drug compounds.

Acromegaly: Overview of Treatment Options

Elevated GH and IGF-I levels are associated with excess mortality and morbidity *(13)*. High GH/IGF-I levels in acromegalic patients are related to a twofold increase in mortality rate when compared to the general population. Achieving GH levels below 1–2 ng/mL and IGF-I values within the normal range for the corresponding age and gender reverses

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Author to whom all correspondence and reprint requests should be addressed: Shlomo Melmed, Cedars-Sinai Research Institute, UCLA David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California. E-mail: melmed@csmc.edu

the excessive mortality rate *(13)*. Uncontrolled acromegaly is linked to increased prevalence of diabetes/glucose intolerance, hypertension, cardiovascular disease, sleep apnea, and arthritis, and the occurrence of these complications decreases with control of GH/IGF-I levels *(14)*. Of note, GH should be suppressed to less than 1 μg/L after an oral glucose load; however, when using recently developed highly sensitive GH assays, the post-glucose cut-off value that most accurately exemplifies biochemical control is 0.4 μg/L or even lower *(15–17)*.

Treatment options for acromegaly include transsphenoidal adenoma resection, pharmacologic therapy with somatostatin analogs, dopamine agonists and GH receptor antagonists, and various modes of radiation therapy. Surgery is the first option of treatment and should be undertaken by an experienced pituitary neurosurgeon. Treatment with somatostatin analogs results in similar rates of GH/IGF-I control in patients who have undergone surgery and in those receiving primary therapy *(11,12,18–22)*, but it represents an expensive life-long treatment. Therefore, the likelihood of surgical success in an individual patient will determine the best initial approach. Surgical excision rapidly alleviates symptoms and removes tumor mass, relieving optic tract pressure effects and headache. Hence, surgery is mandatory in the presence of progressive compressive central symptoms including impaired visual fields related to optic tract pressure effects, because immediate tumor decompression cannot be ensured with other available therapeutic options. Using more stringent criteria for disease control, approx 90% of patients harboring microadenomas (<10 mm) successfully achieved biochemical remission *(23–27)*. When surgical remission is achieved the chances of relapse during follow-up are low, i.e., less than 10% *(24,25,28)*. Unfortunately, most tumors encountered at diagnosis are large macroadenomas, and less than 50% of patients harboring these large adenomas achieve biochemical control *(23,27)*. Recently, Bourdelot et al. *(29)* reported a retrospective analysis of 83 consecutive patients who underwent surgery, observing that high preoperative GH/IGF-I levels, young age, and adenomas with diameter greater than 15 mm, infrasellar extension, supresellar extension above the optic chiasm, or invasiveness (intracavernous extention) assessed by preoperative imaging are predictors of poor surgical outcome. In patients with uncontrolled hormone levels after surgery, medical therapy with somatostatin analogs is the most effective option, resulting in control of excess GH and/or IGF-I in approx 75% of patients *(18,19)*. Dopamine agonist, particularly cabergoline, GH receptor antagonist, and/or pituitary radiotherapy are indicated after failure of somatostatin analog therapy.

Given the overall modest results of surgery in the control of larger GH-secreting adenomas, medical agents have emerged as an option for primary treatment. Clinical features that should be taken into consideration for deciding on primary medical therapy in acromegaly are summarized in Table 1, and indications for primary medical therapy are listed in Table 2.

Somatostatin Analogs

Somatostatin and its analogs act at four levels to target disordered GH secretion: (a) suppression of GHRH secretion from the hypothalamus and (b) of GH secretion from the adenoma, thus indirectly suppressing IGF-I levels, (c) decrease in GH binding to hepatocyte GH receptors and inhibition of hepatic IGF-I synthesis, and (d) prevention of continued pituitary adenoma growth (through apoptosis) which may result in tumor volume reduction *(30,31)*. These actions result in clinical improvement in most patients in whom somatostatin analogs are administered.

Table 3 summarizes studies that evaluated GH/IGF-I lowering effect of somatostatin analogs in patients who had not been subjected to prior surgery or radiotherapy. GH was lowered to safe levels in up to 80% and IGF-I levels were normalized in up to 70% of patients. Although there are no definitive predictors of biochemical responsiveness to somatostatin analogs, some variables provide useful information. Pretreatment GH levels greater than 50 mU/L (equivalent to 20–25 μg/L) are associated with the lowest chance of achieving normalized IGF-I levels *(10)*. Short-term responses may also be helpful; Cozzi et al. *(18)* noted that patients who ultimately achieved target GH and IGF-I levels had GH levels below 5 μg/L after 3 mo and IGF-I levels below 550 μg/L after 6 mo of pharmacotherapy. Importantly, tachyphylaxis was not observed for long-acting octreotide-LAR in several long-term studies using as long as 89 mo of treatment *(10,18,21)*.

A compilation of studies analyzing effects of somatostatin analogs on regression of *de novo* pituitary adenomas has recently been reported *(12)*. Results from 14 selected studies showed that 36.6% (155 of 424) of acromegalic patients receiving primary therapy with somatostatin analogs demonstrated a significant shrinkage in tumor size. The definition of "significant shrinkage" ranged from 10% to >45%. Secondary therapy with octreotide LAR is associated with lower odds of tumor shrinkage than primary octreotide *(32)*. The effect of somatostatin analogs on GH-secreting tumor size is not predicted by biochemical parameters. The percentage change in tumor size does not correlate with percentage reduction in IGF-I or GH levels *(9,20)*. There was also no relationship between the size of the tumor and the degree of tumor shrinkage, as significant tumor regression was documented in both macro- and microadenomas *(9, 20)*. Colao et al. *(11)* reported that in *de novo* patients decompressive effect of octreotide LAR was progressive during long-term treatment, although the most dramatic tumor reduction was observed at 3-mo follow-up (30% after 3 mo vs 8%, 19%, and 5% after 6, 12, and 24 mo, respectively).

The two commercially available somatostatin analogs, octreotide and lanreotide, preferentially bind somatostatin

Table 1
Deciding the Ideal Primary Therapy for Patients Harboring GH-Secreting Adenomas:
Factors to Consider When Choosing Between Surgery and Somatostatin Analogs

	Transphenoidal surgery	Long-acting somatostatin analogs
Cost	One-time cost (when cure achieved)	Life-long therapy
Recurrence rate	Up to 10%	No tachyphylaxis reported
Side effects	<10% morbidity (DI, CSF leak, meningitis, severe sinusitis, hypopituitarism); mortality <1%	Transient GI symptoms 25%, asymptomatic gallstones 15%
Reversal of compressive effects	Tumor excision leads to immediate relief of optic tract pressure and is mandatory for progressive deterioration of visual fields.	Some degree of tumor shrinkage occurs in most patients; a decrease in volume >25 and >50% occurs in approx 50% and approx 25% of patients, respectively.
Biochemical control	70–90% of microadenomas <50% of macroadenomas	50–80% overall
Anesthetic/surgical risk	Avoid surgery if high risk	
Patient preference	Weigh up informed risks vs benefits	Weigh up informed risks vs benefits

DI, diabetes insipidus; CSF, cerebrospinal fluid.

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Table 2
Indications for Primary Medical Treatment
in GH-Secreting Pituitary Adenomas

- Poor likelihood of surgical cure
- Patient frailty
- Unacceptable anesthetic/surgical risk
- No compressive sellar features
- Patient declines surgery

Adapted from: Donangelo, I. and Melmed S. (2005). In: *Transsphenoidal surgery.* Laws, E. R. and Lanzino, G. (eds.). Elsevier: Philadelphia.

receptor (SSTR 2), and with lesser affinity SSTR3 and 5, but not SSTR 1 and 4 *(33)*. Most GH-secreting adenomas express SSTR 2 and SSTR 5. Recently, Freda et al. *(32)* performed a meta-analysis evaluating efficacy of long-acting somatostatin analogs in acromegaly. Their study showed that control of GH/IGF-I levels and tumor shrinkage was attained in a greater proportion of patients treated with octreotide LAR than lanreotide SR. SOM230 is a newly developed multireceptor somatostatin analog with different binding affinity than octreotide and lanreotide. SOM230 binds with high affinity to SSTR 1,2,3, and 5, but not to SSTR4. SSTR4 is either not expressed, or expressed at very low levels in the pituitary and pituitary adenomas; therefore, SOM230 would be predicted to show a similar efficacy to natural somatostatin (SRIF). In pituitary adenoma cultures, this multireceptor ligand has shown equivalent inhibitory effect on pituitary hormone secretion as SRIF and octreotide *(34)*. However, significant decreased GH secretion was observed in more GH-secreting adenoma cultures treated with SOM230 when compared to octreotide, suggesting that SOM230 has the potential to increase the number of patients with acromegaly that can be biochemically controlled *(35)*. A study that compared acute effects of SOM230 and octreotide in patients with acromegaly showed that the former drug was more efficacious in suppressing GH than octreotide in 3 of 12 patients, while in 8 patients, effects where similar and in 1 patient octreotide was superior *(36)*. Different patterns of response likely reflect diverse density and/or expression of tumor SSTR subtypes. The high affinity of SOM230 on more SSTRs may in theory lead to an important clinical role for this analog in managing patients with GH-secreting adenomas resistant to octreotide. This question, as well as whether SOM230 controls pituitary adenoma size, are currently being addressed in clinical studies.

Dopamine Agonists

Dopamine agonists are adjuvant options for treating GH-secreting adenomas, particularly those that co-secrete PRL. Abs et al. *(37)* reported that high doses of cabergoline resulted in GH levels of <2 μg/L in 44% and normalization of IGF-I levels in 35% of patients. Control rates increased to >50% in patients with tumors secreting both GH and PRL. Importantly, biochemical control was related to lower pretreatment hormonal levels, i.e., IGF-I < 750 μg/L. Addition of dopamine agonist (mainly cabergoline) to long-acting somatostatin analogs showed effectiveness in reducing GH/IGF-I levels in resistant patients, even when pre-treatment prolactin levels were within normal range *(38,39)*. Bromocriptine results in IGF-I normalization in only 10% of patients *(40)*, and is not generally recommended for the treatment of this tumor subtype. In summary, cabergoline may play an adjuvant role in the treatment of GH-secreting adenomas. Since GH/IGF-I lowering effects and tumor shrink-

Table 3
Biochemical Efficacy of Primary Somatostatin Analog Therapy for Acromegaly

Reference	Drug in use	Length of use	Patient number	Pretreatment		Post treatment		Normalization of GH levels	Normalization of IGF-I levels
				GH level	IGF-I level	GH level	IGF-I level		
Newman et al., 1998	Octreotide	Mean of 34 mo (3–60 mo)	26	32.7 ± 5.4 μg/L	5.2 ± 0.5 × 10^3 U/L	6.6 ± 1.7 μg/L	2.2 ± 0.3 × 10^3 U/L	43% (a)	17 of 25 (68%) (b)
Amato et al., 2002	Octreotide LAR	24 mo	8	52 ± 31.4 mU/L	567.8 ± 179 ng/mL	NA	NA	50%	50%
Bevan et al., 2002	Octreotide followed by Octreotide LAR	48 wk	27	Median 30.7 mU/L (6.7–141.4)	Median 532 for mA and 718 μg/L for MA (n)	Median 1.8 mU/L (0.6–68.5)	Median 243 for mA and 236 μg/L for MA (n)	79% (e)	53% (f)
Colao et al., 2001	Octreotide LAR	24 mo	15	55.1 ± 10.8 μg/L	861 ± 75.2 μg/L	2.3 ± 0.6 μg/L (nadir value)	323.1 ± 34.9 ng/mL	73.3% (g)	53.3%
Cozzi et al., 2003	Octreotide LAR	Mean 30 mo (18–54 mo)	51 (l)	27.7 ± 4 μg/L	833 ± 41 μg/L	2.3 ± 0.2 μg/L	291 ± 21 μg/L	73% (k)	67% (d)
Ayuk et al., 2002	Octreotide LAR	48 wk	34	30.7 ± 5.7 μg/L	764 ± 68 μg/L	2.6 ± 0.4 μg/L	414 ± 31 μg/L	62% (m)	64%
Ayuk et al., 2004	Octreotide LAR or Lanreotide	> 12 mo	10	9.8 ± 3.7 μg/L	592.9 ± 74.7 μg/L	2.6 ± 0.6 μg/L	276.4 ± 33.9 μg/L	50% (i)	50% (f)
Baldelli et al., 2000	SR-Lanreotide	24 mo	23	65.1 ± 11.4 mU/L	638.5 ± 41.5 ng/mL	3.6 ± 0.6 mU/L	255.6 ± 44.6 ng/mL	78% (c)	70% (d)
Amato et al., 2002	SR-Lanreotide	24 mo	12	60.2 ± 30.6 mU/L	565.7 ± 198.7 ng/mL	NA	NA	58.3% (e)	66.7% (f)
Attanasio et al., 2003	Lanreotide 60 mg	Median of 24 mo (6–48 mo)	30(l)	18.2 ± 3.1 μg/L	232 ± 16% ULNR (j)	2.7 ± 0.6 μg/L	93 ± 8% ULNR	63% (k)	70%

(a) GH values of ≤2 μg/L during at least four study visits.
(b) IGF-I within normal range for gender during at least half of the study visits.
(c) Basal GH values < 7.5 mU/L (immunoradiometric assay, IRMA).
(d) IGF-I within the normal range for age (radioimmune assay, RIA).
(e) GH < 5 mU/L (IRMA or chemiluminescent immunometric assay).
(f) IGF-I within normal range for sex and age (IRMA).
(g) GH ≤ 2.5 ng/mL (average value from at least three samples collected 15 minutes apart) [IRMA].
(h) IGF-I within normal range for age (IRMA).
(i) GH values ≤2 μg/L (RIA).
(j) ULNR: upper limit of normal age.
(k) GH < 2.5 μg/L (IRMA).
(l) A fraction of these patients were previously treated with somatostatin analogs. Wash out period of at least 3 mo before starting study drug.
(m) GH < 2.0 μg/L (double monoclonal antibody technique).
(n) mA: microadenoma; MA: macroadenoma.
Adapted from: Donangelo, I. and Melmed S. (2005). In: *Transsphenoidal surgery.* Laws, E. R. and Lanzino, G. (eds.). Elsevier: Philadelphia.

age are not uniformly achieved, therapy with this compound should be reserved for those patients with modest hormone hypersecretion, provided that no tumor-compressive signs are present.

GH Receptor Antagonist

GH receptor antagonist (GHRA), pegvisomant, directly inhibits peripheral GH action. Unlike somatostatin analogs and dopamine agonists that act centrally to inhibit tumor GH secretion and tumor growth through somatotroph-cell somatostatin and dopamine receptors, pegvisomant interferes with functional dimerization of two GH receptor subunits inhibiting the signal for IGF-I production *(41)*. Pegvisomant suppresses peripheral IGF-I generation in almost all patients harboring GH-secreting pituitary adenomas treated for up to 18 mo. As IGF-I levels decrease to normal range in 97% of the patients, GH levels increase approx twofold during pegvisomant therapy *(42,43)*. GH levels rise during pegvisomant therapy partly because of the release from negative feedback caused by reduction in IGF-I levels and partly because of the drug cross-reaction with GH assays. A concern with prolonged pegvisomant therapy is pituitary tumor growth, which was reported in 2 of 152 patients *(42,43)*. Therefore, it is recommended that patients receiving pegvisomant should have periodic pituitary adenoma images. Significant increase in serum liver enzyme concentration was reported in <1% to 12% of patients *(42–44)*, and for this reason regular liver function testing is mandatory when pegvisomant is used.

An important aspect of treatment with GHRA is that IGF-I level becomes the only biochemical parameter of disease activity and patients may become "GH-deficient." During pegvisomant therapy GH levels are not reliable, as stated above. It is difficult to determine the normal IGF-I levels for an individual patient, and it is well known that adult patients with GH deficiency may have IGF-I levels within the normal range *(45)*. Moreover, adult GH deficiency is clearly associated with increased cardiovascular mortality *(46)*. There is currently no clear way to detect "overtreatment" of acromegaly when using pegvisomant. Intuitively, it is advisable to aim for IGF-I levels within the mid-normal range for age and sex.

Owing to potential side effects and high cost, pegvisomant is not currently recommended as a primary therapy in patients with acromegaly *(47,48)*. Results of long-term follow-up studies should provide more detailed information on unwanted side effects. Studies on pegvisomant show higher rates of IGF-I normalization and superior improvement of insulin resistance caused by high GH/IGF-I levels, when compared to the results obtained with somatostatin analogs *(49–51)*. Conversely, therapy with somatostatin analogs leads to decreased tumor size in approx 50% of patients, does not cause major side effects, and has a lower cost than GHRA. So what is the place of GHRA in the treatment algorithm of acromegaly? The clearest indication for pegvisomant is in patients who do not attain biochemical control with somatostatin analogs *(44,47,52)*, as recently shown by Feenstra et al. *(52)*. In this open-label study, patients with active acromegaly not controlled by somatostatin analog therapy received a combination of pegvisomant and long-acting somatostatin analog. Pegvisomant was administered weekly, and the dose titrated until IGF-I levels were within the normal range (or maximal dose reached). Of 19 patients that completed 42 wk of therapy, 18 (95%) achieved normal IGF-I levels, suggesting that in patients whose IGF-I concentrations cannot be controlled by monthly long-acting somatostatin analog monotherapy, addition of weekly pegvisomant may be effective. Importantly, no signs of pituitary tumor growth was observed over the 6 mo of combination therapy. A safety issue that remains to be clarified is elevated liver transaminases seen in 38% (10 of 19) of patients. Frequency of transaminase elevation with combination of pegvisomant and somatostin analogs is higher than that reported for pegvisomant alone *(42–44)*, and the long-term safety of the combination therapy should be ensured before its overt recommendation.

Somatostatin–Dopamine Chimeric Ligand

Combined treatment of acromegaly with dopamine agonists and somatostatin analogs reduces both GH and IGF-I levels more effectively than treatment with either agonist alone *(38,39)*. Mechanisms by which combined somatostatin–dopamine treatment enhances GH suppression remain unclear, but molecular analysis has demonstrated heterodimerization of somatostatin and dopamine receptors, and it is possible that effects of the combined treatment may involve receptor dimerization and synergistic action *(53)*.

Normal human pituitary and human GH-secreting pituitary adenomas express both dopamine and somatostatin receptors. Co-treatment of rat and human pituitary cells with SSTR2 and dopamine receptor type 2 (DAR2) agonists produces GH suppression similar to *(54)* or greater *(55)* than that produced by activation of either receptor alone. BIM-23A387, a chimeric compound with potent binding to both DAR2 and SSTR2, showed comparable or greater effectiveness in suppressing GH secretion in human fetal pituitary and GH-secreting adenoma cells compared to SSTR2 and DAR2 agonists added in combination *(54,55)*. DAR2 antagonist (sulpiride), but not SSTR2 antagonist (BIM-23454) blocked BIM-23A387 GH suppression *(55)*, suggesting a functional interaction between both SSTR2 and DAR2 is required for the GH lowering effect of this chimeric compound. Thus, BIM-23A387 represents a new drug that may be useful in the treatment of patients with acromegaly and hyperprolactinemia. Patients whose adenomas express both SSTR2 and DAR2 are especially suitable and should benefit from this compound.

Conclusion

Medical treatment of acromegaly has significantly improved over the last years, essentially due to development of molecules that target adenomatous GH cell actions. As the knowledge on mechanisms of pituitary tumor initiation and progression evolves, targeted therapy will advance and hopefully safe options that fulfill goals of treatment will be conceived.

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