Pharmacological management of acromegaly: a current perspective

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Acromegaly is a chronic disorder of enhanced growth hormone (GH) secretion and elevated insulin-like growth factor-I (IGF-I) levels, the most frequent cause of which is a pituitary adenoma. Persistently elevated GH and IGF-I levels lead to substantial morbidity and mortality. Treatment goals include complete removal of the tumor causing the disease, symptomatic relief, reduction of multisystem complications, and control of local mass effect. While transsphenoidal tumor resection is considered first-line treatment of patients in whom a surgical cure can be expected, pharmacological therapy is playing an increased role in the armamentarium against acromegaly in patients unsuitable for or refusing surgery, after failure of surgical treatment (inadequate resection, cavernous sinus invasion, or transcapsular intraarachnoid invasion), or in select cases as primary treatment. Three broad drug classes are available for the treatment of acromegaly: somatostatin analogs, dopamine agonists, and GH receptor antagonists.

Somatostatin analogs are considered as the first-line pharmacological treatment of acromegaly, although efficacy varies among the different formulations. Octreotide long-acting release (LAR) appears to be more efficacious than lanreotide sustained release (SR). Lanreotide Autogel (ATG) has been shown to result in similar biological control as octreotide LAR, and there may be a benefit in switching from one to the other in some cases of treatment failure. The novel multireceptor somatostatin analog pasireotide, currently in Phase II clinical trials, also shows promise in the treatment of acromegaly. Dopamine agonists have been the earliest and most widely used agents in the treatment of acromegaly but have been found to be less effective than somatostatin analogs. In this class of drugs, cabergoline has shown greater efficacy and tolerability than bromocriptine. Dopamine agonists have the advantage of oral administration, resulting in increased use in select patient groups. Selective GH receptor antagonists, such as pegvisomant, act by blocking the effects of GH, resulting in decreased IGF-I production despite persistent elevation of GH serum levels. Thus far, tumor growth has not been a concern during pegvisomant therapy. However, combination treatment with somatostatin analogs may counteract these effects. The authors discuss the latest guidelines for biochemical cure and highlight the efficacy of combination therapy. In addition, the effects of pharmacological presurgical treatment on surgical outcome are explored. (DOI: 10.3171/2010.7.FOCUS10168)

**Key Words** • acromegaly • octreotide • lanreotide • pasireotide • pegvisomant • growth hormone

Acromegaly is a chronic disorder characterized by elevated GH secretion with a resultant increase in serum IGF-I level. A pituitary adenoma is the most common cause of the disorder. Persistently elevated levels of GH and IGF-I lead to significant morbidity and mortality. Complications of acromegaly include, but are not limited to, acral growth, cardiovascular disease, insulin resistance and diabetes, arthritis, hypertension, and sleep apnea. All of these adverse complications individually and collectively lead to a shortened life span. With GH-secreting tumors being the most common cause of acromegaly, other symptoms related to the tumor itself are often present in patients with these lesions. These symptoms include headaches and visual disturbances due to the mass effect on the optic nerve and chiasm.

*Abbreviations used in this paper: ATG = Autogel; GH = growth hormone; GHRH = GH-releasing hormone; IGF = insulin-like growth factor; LAR = long-acting release; SC = subcutaneous; SR = sustained release.*
Progressive expansion of GH-secreting tumors can also lead to loss of pituitary function and variable degrees of hypopituitarism. In children, in whom the epiphyseal growth plate is not closed, excessive GH secretion leads to progressive linear growth as the predominant symptom, clinically manifesting as gigantism.

The goals of treatment should include complete tumor removal, alleviation of symptoms, and control of complications. Control of excessive GH secretion can be achieved through surgical removal of the tumor, radiotherapy, and medical treatment. In this review, we examine the pharmacological management of acromegaly, with a focus on the efficacy and side-effect profile of medical therapy.

Pathophysiology of Acromegaly

The molecular genetics of tumorigenesis in acromegaly have been recently elucidated. Development and differentiation of somatotrophs, GH-producing cells in the anterior pituitary, are influenced by a gene named the Prophet of Pit-1 (PROP1), which is responsible for the embryological development of the cells of the Pit-1 (POU1F1) transcription factor lineage. The binding of Pit-1 to the GH promoter in the cell nucleus results in development and growth of somatotrophs and subsequent GH transcription. Growth hormone is a 191–amino acid polypeptide synthesized and secreted in a pulsatile fashion by the anterior pituitary. Growth hormone–releasing hormone (GHRH) stimulates the synthesis and secretion of GH while somatostatin inhibits GH release, with both traveling in the portal vein and acting on somatotroph-specific transcription factors (Fig. 1). The effects of GH are mediated by GH receptors found primarily in the liv-
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er and cartilage. Activation of the GH receptor results in phosphorylation of the receptor and Janus kinase 2 (JAK2) followed by the binding of signal transducer and activator of transcription (STAT) proteins to the complex. The STAT proteins then become phosphorylated, translocate into the cell nucleus, and initiate transcription of target proteins, such as IGF-I, which induces cell proliferation and inhibits apoptosis. The development of a GH-secreting tumor is the result of variables that affect the development and growth of somatotrophs and their hormone production. Approximately 40% of tumors appear to harbor a mutation in the α-subunit of the Gs protein that results in constitutive activation of cyclic AMP. Overexpression of the pituitary tumor–transforming gene (PTTG) protein and loss of expression of the growth arrest and DNA damage-inducible (GADD) 45α protein, a proapoptotic factor, has been demonstrated in GH-secreting pituitary adenomas. Overproliferation of somatotrophs and the resultant excessive secretion of GH results in acromegaly.27

The majority of somatotroph tumors are macroadenomas, but there have been rare instances of pituitary carcinomas. Up to 40% of GH-secreting pituitary adenomas cosecrete other pituitary hormones, especially prolactin and thyrotropin, leading to additional clinical manifestations. Other rare causes of primary GH excess include familial syndromes, such as Carney syndrome, multiple endocrine neoplasia Type I, McCune-Albright syndrome, and familial acromegaly. Extrapituitary causes of excess GH can result from ectopic hypersecretion of GH by pancreatic islet-cell tumors or lymphoma. Finally, GH excess can result from somatotroph hyperplasia due to excess GHRH production by central hypothalamic tumors or peripheral neuroendocrine tumors (Fig. 2).27

Biochemical Criteria for Diagnosis of Acromegaly

Acromegaly is diagnosed by finding an elevated IGF-I level compared with the age- and sex-adjusted normal range and a failure to suppress GH in response to an oral glucose tolerance test (OGTT). Unlike normal subjects, patients with acromegaly do not suppress GH secretion to very low levels with a glucose load. A post-OGTT GH level of less than 1.0 μg/L is the most recent cutoff level used to separate individuals without acromegaly from those with the disorder. As newer and more sensitive immunological assays become available, the cutoff points to define acromegaly may need to be adjusted accordingly.13,18

Overview of the Management of Acromegaly

Treatment of this disease requires optimal interaction between the management team members. Our focus in this article will be on patients with GH-secreting adenomas because they represent more than 98% of cases of acromegaly. All authorities in the field believe that surgery by an experienced neurosurgeon is the treatment of choice for GH-secreting adenomas. In experienced hands, this treatment leads to disease control in 50% of patients. Some patients, however, might refuse surgery or could be poor candidates for this procedure. In addition, there are a large number of patients in whom surgery is not curative and who would require additional treatment. Available options

Fig. 2. Causes of acromegaly: excessive GH or GHRH. Reproduced with permission from Melmed S: Medical progress: acromegaly. N Engl J Med 355:2558–2573, 2006. Copyright © 2006 Massachusetts Medical Society. All rights reserved.
include various forms of irradiation and medical therapy. While radiation therapy can be effective, it takes years to show its benefits in controlling GH secretion. Thus, even patients given all forms of radiation therapy would require additional treatments to control GH secretion until radiation effects become apparent. With the availability of newer and more effective agents, the focus on medical therapy has intensified to the point that some researchers and practitioners advocate it to be the primary therapy in most patients. The following section will address available medical therapies and their efficacies, advantages, and disadvantages.

**Somatostatin Analogs**

First introduced in the 1980s, somatostatin analogs have been widely used in the treatment of acromegaly. The concept is to mimic the physiological inhibitory action of somatostatin on the anterior pituitary gland. Two endogenous, biologically active forms of somatostatin are formed by the cleavage of prosomatostatin: SRIF-14 and SRIF-18. Twenty-five different somatostatin receptor subtypes, sst1–5, have been characterized. These subtypes are 7-transmembrane domain G-protein–coupled receptors. The importance of delineating the subtypes becomes apparent when one considers the expression profile in normal pituitary gland and pituitary adenomas as well as the receptor selectivity of drugs. Studies have shown that the human pituitary gland primarily expresses the sst1, sst2, sst3, and sst5 receptors. Additionally, GH secretion by human fetal somatotroph cells appears to be regulated by the sst1 and sst5 receptors. When pituitary adenomas were investigated, the sst1, sst2, sst3, and sst5 receptor subtypes were also shown to be expressed. Additionally, most human GH-secreting pituitary tumors primarily express the sst1 and sst2 receptors.

Octreotide SC was the first somatostatin analog available for clinical use. Initial dosage is 100 µg injected subcutaneously 3–4 times daily, titratable to a maximum of 1.5 mg/day. The dosing regimen of 3–4 times daily is required to maintain therapeutic serum levels because of the 2-hour half-life. To reduce the inconvenience of multiple injections per day and increase compliance, long-acting formulations have been developed. Octreotide LAR was the first long-acting formulation and is based on octreotide delivered in polymeric microspheres. The starting dosage is 20 mg intramuscular injection every 4 weeks and can be titrated up to 40 mg. Octreotide has been shown to act primarily at the sst2 receptor subtype. Lanreotide was the second long-acting somatostatin analog developed and is available in 2 formulations: lanreotide SR and lanreotide ATG. Lanreotide ATG is currently the primary formulation of lanreotide currently used clinically, but there are only a handful of studies comparing the efficacies of octreotide LAR and lanreotide ATG. Results from nonrandomized open-label studies have suggested that lanreotide ATG is at least as effective as octreotide LAR. A randomized crossover trial by Andries and colleagues further supports the findings of equal efficacy between octreotide LAR and lanreotide ATG. Additionally, their study suggests that some patients who experience treatment failure or adverse effects may benefit from a switch between the 2 drugs. Pasireotide, which is currently in Phase II clinical trials, has demonstrated biochemical control in 27% of patients after 3 months of treatment in a recent study. As the authors of this randomized multicenter trial have reported, the study was not designed or powered to compare the efficacy of pasireotide to octreotide, which was first self-administered for 28 days. However, pasireotide shows promise as a new treatment for acromegaly.

Another important parameter to consider in the medical management of acromegaly is the effect on tumor shrinkage. A number of studies have investigated the antitumor effects of somatostatin analogs, and their data has been examined in various reviews. From a total of 22 studies, Bevan found that 217 (45%) of 478 patients who were treated with octreotide SC had significant tumor shrinkage. It was also noted that tumor shrinkage was seen in 110 (51%) of 217 patients treated primarily with octreotide SC compared with 22 (27%) of 82 patients who received octreotide adjunctively after surgery and/or radiation treatment. Freda and colleagues showed that, of 468 patients treated with octreotide SC, 40.8% had significant decreases in tumor size. In considering studies involving octreotide LAR treatment, tumor size reduction was shown in 103 (57%) of 180 patients. As with octreotide SC, primary treatment with octreotide LAR resulted in a higher percentage of patients with tumor shrinkage than secondary treatment did (80% vs 28%). Studies of lanreotide SR showed decreases in tumor size in 62 (24%) of 263 patients. As with the other drugs, primary therapy with lanreotide SR showed a greater degree of tumor-size reduction than secondary therapy (31% vs 9%). The caveat is that, in a few of the octreotide LAR studies, patients were preselected...
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for drug responsiveness, which could falsely elevate the response rate. When data were combined from all the studies, 382 (42%) of 920 patients had a decrease in tumor size. Again, primary therapy showed a more pronounced effect on tumor shrinkage than secondary therapy did (52% vs 21%). The meta-analysis by Freda and colleagues supports the general finding that primary treatment results in higher rates of tumor shrinkage than secondary treatment. Melmed and colleagues reported similar findings in a review, noting that significant tumor reduction was found in 36.6% of 424 patients receiving primary somatostatin treatment. Bevan suggested that this observation may be the result of alterations in tumor anatomy, such as fibrosis or scarring, caused by prior surgery or radiotherapy. Overall, among the different somatostatin analogs, octreotide LAR has shown greater rates of tumor size reduction than octreotide SC and lanreotide SR.

The side-effect profile and safety of somatostatin analogs has been well studied. Generally, they are well tolerated and fairly safe. Among the side effects, gastrointestinal symptoms, including nausea, diarrhea, and abdominal pain, are the most commonly reported. Biliary tract abnormalities, such as biliary sludge and cholelithiasis, have also been known to occur. In addition, somatostatin analogs have the potential to impair the secretion of insulin, which is of particular concern in acromegaly, a condition that already has an increased risk of impaired glucose tolerance and diabetes.

Dopamine Agonists

Like somatostatin analogs, the dopamine agonists inhibit GH secretion in pituitary tumors but do so by binding to D2 receptors. Dopamine receptors exist in 5 subtypes with specific distribution in tissue. D2 receptors are found in the anterior and intermediate lobes of the pituitary. Bromocriptine, a nonselective dopamine agonist, was the first to be widely used since it became available in 1974. Unfortunately, it has been found to be less effective when compared with somatostatin analogs. Additionally, acromegaly—as compared with prolactinomas—requires more frequent and higher doses of bromocriptine for treatment. Cabergoline, a more selective D2 receptor agonist, has a longer half-life (62–115 hours) and demonstrated better efficacy and tolerability. Other dopamine agonists, such as lysuride, pergolide, quinagolide, and terguride, have been studied but were found to be less effective than bromocriptine and cabergoline.

Dopamine agonists, however, have advantages over other pharmacological treatments. They can be taken orally as opposed to requiring injection, and are perhaps less expensive than octreotide. These drugs can be used alone or as an effective adjunct to somatostatin analog therapy. Among all GH-secreting adenomas, dopamine agonists are the most effective in patients with pituitary tumors that cosecrete prolactin or thyrotropin.

Side effects of dopamine agonists include constipation, nausea, postural dizziness, and nasal congestion. The adverse responses can be minimized if the drug is started at a low dose with a slow increase and taken with food. It should be noted that, in patients with Parkinson disease, there is evidence that the high dose of cabergoline used for treatment is associated with valvular heart disease. While cardiac abnormalities have not been demonstrated in patients with pituitary adenomas on cabergoline, monitoring patients receiving higher than regular doses is recommended.

Chimeric Compounds

Dopamine agonists have been reported to suppress GH levels in some patients with acromegaly. Furthermore, the combination of a somatostatin analog and a dopamine agonist has been suggested to work synergistically. Rocheville and colleagues demonstrated that somatostatin and dopamine receptors can form hetero-oligomers with enhanced receptor activity. Several chimeric molecules with both somatostatin and dopamine receptor affinity have been developed. BIM23A387, which has selective binding to sst2 and D2 receptors in cultured somatotropic tumor cells, has been shown to have greater GH suppression compared with an individual agonist or a combination. To date, there have been no published clinical studies for BIM23A387. Another chimeric molecule, BIM23A760, has an affinity for sst2, sst5, and D2 receptors. It has demonstrated more potent inhibition of GH secretion than sst2, sst5, and D2 agonists and pasireotide. A variety of other novel chimeric molecules have been investigated and show potential for treatment.

Growth Hormone Receptor Antagonists

Pegvisomant represents the first in a novel class of drugs that act on GH receptors. It is a genetically engineered, pegylated analog of human GH that functions as a selective GH receptor antagonist. Pegvisomant competes with physiological GH for binding, thus preventing receptor dimerization and signaling, resulting in decreased IGF-I production. The mechanism of action blocks the effects of excessive GH instead of inhibiting its secretion and so can function independent of tumor receptor expression or type. Because the drug is pegylated, it has an increased half-life of approximately 6 days and a reduced possibility of antibody formation. Pegvisomant is available in 10-, 15-, and 20-mg SC injections. The initial loading dose is a 40-mg SC injection; it is followed by maintenance dosages of 10 mg daily, adjustable to a maximum maintenance dose of 30 mg daily.

Trainer and colleagues investigated the efficacy of pegvisomant in a 12-week randomized placebo-controlled study of 112 patients with acromegaly. They reported a dose-dependent normalization of serum IGF-I levels, with 89% of patients in the 20-mg daily dose group and improvements in clinical symptoms in all pegvisomant-treated groups. Another study found similar results when analyzing the long-term efficacy of pegvisomant in 160 patients treated for up to 18 months. The investigators report that 87 (97%) of 90 patients treated for at least 12 months attained normal serum IGF-I levels. In a recent study from the German Pegvisomant Observational Study, 76.3% of patients treated with pegvisomant for 24 months had normal IGF-I levels.

Because pegvisomant blocks GH from binding to its receptor instead of suppressing GH secretion by the pituitary tumor, there has been concern for potential tumor
growth as a result of an interruption in GH-mediated negative feedback inhibition on the tumor. A rise followed by a plateau of serum GH levels echoing the reduction in serum IGF-I with no significant change in tumor size has been reported during treatment. A recent prospective multicenter study designed to investigate tumor volume during long-term therapy found similar results, with an increase in tumor size (> 25%) in only 3 (4.9%) of 61 patients. Pegvisomant has been found to be generally well tolerated. One often-reported adverse reaction is elevated levels of alanine transaminase and aspartate transaminase. In patients with elevated liver enzyme levels, some had transient abnormal values that normalized during treatment while others had enzyme levels that returned to normal following discontinuation of pegvisomant. It has been recommended that liver function tests be performed regularly during treatment. Injection-site lipohypertrophy has also been experienced, though it resolves with more frequent injection-site change. Other adverse reactions include hypercholesterolemia, infections, and self-limited injection-site erythema.

**Primary or Secondary Pharmacological Therapy**

According to the recent consensus statement on management by the Acromegaly Consensus Group, transsphenoidal surgery is still considered first-line treatment for intrasellar microadenomas, noninvasive macroadenomas, and adenomas resulting in compression symptoms. Reports indicate that surgical excision achieves normalization of serum IGF-I in 75%–95% of patients with microadenomas and 56%–68% of patients with noninvasive macroadenomas. Remission rates drop when surgical removal of invasive macroadenomas is considered. Primary pharmacological therapy may be indicated in such patients and in those who are otherwise poor surgical candidates. While studies designed to investigate the use of primary pharmacological therapy are limited, the use of drugs in treatment-naive patients may be efficacious.

In a study comparing octreotide as primary treatment versus octreotide as secondary therapy after surgery or radiation, Newman and colleagues reported equal efficacy with octreotide as primary or secondary therapy. A retrospective study investigating the efficacy of octreotide LAR as primary and adjunctive therapy also found similar efficacy. In an open prospective multicenter trial, Colao and colleagues demonstrated that, in patients with micro- and macroadenomas, primary octreotide LAR treatment controlled hormone excess, reduced tumor volume, and improved symptoms. In another study, Colao and colleagues investigated the effects of octreotide LAR and lanreotide ATG on tumor-size reduction in treatment-naive patients. A reduction in tumor size of at least 25% was observed in 75.5% of patients after 12 months of primary therapy with a somatostatin analog. The authors also found that the best predictor of tumor reduction was the posttreatment serum IGF-I level.

The use of primary pharmacological treatment also has the potential to influence surgical outcome positively. In a prospective randomized trial, Carlsen and colleagues reported that 6-month pretreatment with octreotide improved surgical cure rates in patients with macroadenomas compared with those who had direct surgery without pretreatment (50% vs 16%). However, they observed no benefit of pretreatment and possibly an adverse effect in patients with microadenomas. Yin and colleagues reported similar results in patients treated with octreotide LAR for 3 months prior to transsphenoidal tumor resection. In a retrospective study, Colao and colleagues concluded that 3–6 months of presurgical octreotide treatment improved clinical symptoms and surgical outcomes and decreased hospitalization time postoperatively. Other studies, however, showed no benefit. Further investigation is needed to define the role of presurgical pharmacological treatment in acromegaly.

**Combination Pharmacological Therapy**

Another area of study that shows promise in the management of acromegaly is the use of drug combinations. As discussed earlier, pegvisomant can result in increased serum GH levels. Additionally, there is the concern of tumor growth during therapy. By adding a somatostatin analog to the treatment regimen, one may be able to reduce serum GH levels and reduce tumor size, potentially counteracting the shortcomings of pegvisomant. A recent review by Neegers and van der Lely examined the long-term efficacy and safety of pegvisomant and somatostatin analog combination therapy. They concluded that treatment was effective in normalizing serum IGF-I levels in more than 90% of patients. Additionally, they found that combination therapy resulted in tumor reduction in approximately 20% of patients, which is not seen in pegvisomant monotherapy. The addition of dopamine agonists to somatostatin analog therapy has also been shown to increase the efficacy of treatment in some patients (Table 1).

**Cost of Pharmacological Management**

Previous studies on economic burden in the management of acromegaly have revealed that the cost of medication represents the greatest contribution (38%) and exceeds the cost of surgery. An accurate comparison of the cost of the various pharmacological agents mentioned above would be extremely difficult due a myriad of reasons: microadenoma versus macroadenoma (the latter costs more than double the cost of the former), variations in the physician’s choice of drug management, and economic determinates, such as health care systems and currency value.

**Conclusions**

Pharmacological management plays a pivotal role in the treatment of acromegaly. Somatostatin analogs, particularly the long-acting formulations, are considered first line in medical therapy and have shown to result in the reduction and normalization of GH and IGF-I levels. In addition, they have been found to reduce pituitary tumor size. Dopamine agonists, while less effective than somatostatin analogs, have certain advantages, including oral administration. When added to somatostatin analog therapy, dopamine agonists may increase efficacy of treatment. Growth
TABLE 1: Pharmacological therapy of acromegaly*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Somatostatin Analogs</th>
<th>Dopamine Agonists</th>
<th>GH Receptor Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>indications</td>
<td>1st-line therapy in cases w/ low expectation of surgical cure (large extrasmall tumors); postop/lack of biochem control; to achieve partial disease control prior to radiation therapy for acromegaly</td>
<td>patient preference of oral medication &amp; cost factors; patient w/ markedly elevated prolactin w/ GH &amp; IGF-I; combination therapy w/ somatostatin analogs in refractory cases</td>
<td>persistent high IGF-I levels despite max treatment w/ other modalities; included in combination therapies</td>
</tr>
<tr>
<td>dosage</td>
<td>octreotide SC: 100 μg SC 3 × daily (max 1.5 mg daily); octreotide LAR: 20 mg IM every 4 wks (max 40 mg); lanreotide SR: 30 mg IM every 7–14 days; lanreotide ATG: 60, 90, &amp; 120 mg deep SC every 4 wks</td>
<td>cabergoline: 1–4 mg orally weekly</td>
<td>pegvisomant: 40 mg SC loading dose, 10 mg daily maintenance dose (max 30 mg daily)</td>
</tr>
<tr>
<td>biochem control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH &lt; 2.5 mg/L</td>
<td>~70%</td>
<td>&lt;15% (cabergoline)</td>
<td>↑ GH (pegvisomant)</td>
</tr>
<tr>
<td>normalization of IGF-I</td>
<td>~70%</td>
<td>&lt;15% (cabergoline)</td>
<td>&gt;90% (pegvisomant)</td>
</tr>
<tr>
<td>onset of response</td>
<td>rapid</td>
<td>slow</td>
<td>unchanged</td>
</tr>
<tr>
<td>tumor mass shrinkage</td>
<td>~ 50%</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>adverse effects</td>
<td>biliary tract disease (biliary sludge, cholelitiasis); impaired glucose tolerance &amp; diabetes; GI symptoms (nausea, vomiting, ab pain)</td>
<td>GI symptoms; postural dizziness; nasal congestion; valvular heart disease;↑ LFTs; injection-site lipohyper trophy; hypercholesterolemia</td>
<td></td>
</tr>
</tbody>
</table>

* ab = abdominal; biochem = biochemical; GI = gastrointestinal; IM = intramuscular; LFT = liver function test; ↑ = elevated.

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The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Manjila. Acquisition of data: Manjila, Wu. Analysis and interpretation of data: Manjila, Wu. Drafting the article: Manjila, Wu, FR Khan, MM Khan. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: Selman, Manjila.

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somatotropinomas and correlation to in vivo hormonal and tumor volume responses to treatment with octreotide LAR. 


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