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Somatostatin Analogs in Medical Treatment of Acromegaly

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Although acromegaly remains a disease primarily addressed by pituitary microsurgery, most patients require secondary treatment for persistent growth hormone (GH) hypersecretion and elevated serum insulin-like growth factor-1 (IGF-1) concentrations following adenomectomy. Persistently abnormal serum GH and IGF-1 can be reduced to normal concentrations in better than half of post-surgery acromegalics using the pharmacologic treatments available at present, the dopamine agonists (DA) and somatostatin (SST) analogs. The long-acting SST analogs octreotide LAR and lanreotide SR have become the mainstay of medical treatment for acromegaly, having largely supplanted DA agents since the introduction of bromocriptine for the suppression of GH secretion in the 1970s. The DA cabergoline may be effective in up to half of patients, however, in particular those patients whose tumors cosecrete prolactin. On the horizon is the GH-receptor antagonist pegvisomant, which is expected to enable the reduction of serum IGF-1 to the normal range in the vast majority of postoperative acromegaly patients, representing a revolutionary development in the medical treatment of this disease. We here review the choices available to the endocrinologist in the pharmacologic treatment of acromegaly, focusing upon the SST analogs.

Key Words: Somatostatin analog; acromegaly; pegvisomant; cabergoline; insulin-like growth factor-1; growth hormone.

Introduction

The term *acromegaly* first appeared in the medical literature in 1886 when Pierre Marie described the syndrome and named it to reflect its unique phenotype of acral overgrowth *(1)*. Over the century that followed, accumulated experience with acromegaly brought to light numerous morbidities of greater consequence than the evident coarsened facial features, including arthropathy; hypertension; cardiomyopathy; obstructive sleep apnea; diabetes mellitus; and, perhaps, increased propensity for neoplastic disease. Local perisellar and hormonal effects of pituitary tumor mass, such as optic chiasmal impingement and hypopituitarism, also became apparent.

For decades, primary treatment of acromegaly has been aimed at surgical extirpation of the somatotrope adenoma. Radiotherapy has been used as a primary or secondary therapeutic modality since early in the last century. Beginning in the 1970s, bromocriptine was distinguished as the first medication to be employed for control of disease status. In the last two decades, the rapid development of superior strategies for medical management has advanced steadily and gained ground on surgical treatment. Indeed, it is reasonable to speculate that pharmacologic management, as it has in the treatment of prolactinomas, may eventually surpass transsphenoidal surgery for primary treatment of acromegaly, a prospect that seems most plausible in the case of unresectable macroadenomas.

In this article, the medical approaches to treatment of the acromegalic syndrome are examined in order of chronological appearance. Dopamine agonist therapy was the first medical strategy for the treatment of acromegaly, and, although it is the least effective, it remains an occasionally useful alternative to the more expensive peptidic preparations. Somatostatin analog therapy became available in the 1980s and has become the mainstay of medical treatment for acromegaly, having fulfilled a need for a sizable cohort of patients with persistent growth hormone (GH) oversecretion following surgery. Finally, and representing a new paradigm in the treatment of the disease, the GH receptor (GHR) antagonist pegvisomant is examined, with a review of early trial results.

Background

Acromegaly is an uncommon disease, with an estimated prevalence of 1 in 20,000 to 25,000 persons *(2,3)*. In the great majority of cases, acromegaly is caused by hypersecretion of GH from a monoclonal somatotrope adenoma *(4)*, the third most common type of pituitary tumor, behind prolactinomas and nonfunctioning adenomas. Mutations in the α-subunit of the G_s protein have been found in 40% of somatotrope adenomas from patients with clinical acromegaly *(5)*.

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Under the influence of GH hypersecretion, both systemic and, likely, local production of insulin-like growth factor-1 (IGF-1) is augmented, which ultimately furnishes the growth-promoting stimulus. The soft-tissue growth caused by elevated IGF-1 is manifested by arthralgias and peripheral poly-neuropathy, expansion of hand and foot soft-tissue mass marked by increased ring and shoe size, progressive coarsening of facial features marked by prognathism and dental separation, and prominence of supraorbital ridges. Skin tags and hyperhidrosis are common, as are excessive snoring and obstructive sleep apnea. Cardiovascular effects include left ventricular hypertrophy and hypertension. The incidence of neoplastic disease is likely increased, and glucose intolerance and hyperinsulinemia manifest alterations in carbohydrate metabolism. Among the direct physical effects of tumor mass is optic chiasmal compression producing visual field defects, and other destructive effects such as cerebrospinal fluid (CSF) rhinorrhea and cranial nerve palsies may follow local extension or invasion of cavernous sinuses.

Any treatment strategy must address the same goals, which include the relief of symptoms, decompression of the sella turcica with preservation of pituitary function, and normalization of circulating IGF-1 and of the mortality rate. Transsphenoidal adenomectomy remains the standard first-line treatment of acromegaly. Operative complications such as CSF leak, meningitis, sinusitis, and new hypopituitarism are very uncommon, overall about 8%, provided that the procedure is undertaken by surgeons with extensive experience *(6–8)*. Despite improved surgical techniques and outcomes, a substantial proportion of patients with acromegaly will require some kind of adjunctive therapy following surgery to reduce IGF-1 levels to a nonthreatening level. Among surgeons with extensive experience, the reported cure rate for GH-secreting microadenomas is very close to 90% *(7,8)*, though clearly this represents the best clinical practice, and is not likely a widely attainable mark. Furthermore, less than one in three GH-secreting tumors meet the diagnostic criterion of a microadenoma (under 10 mm in diameter) at the time they are detected, and acromegaly owing to a GH-secreting macroadenoma, representing the majority of patients, is brought into remission by surgery alone in <50% of cases *(6–8)*.

The biochemical parameters outlining normal GH secretion have become increasingly rigorous as the definition of cured acromegaly has simultaneously become less certain. The early primary focus on symptom relief has yielded to a more stringent scrutiny of postoperative biochemical findings, as newer assays for GH and IGF-1 have revealed the complexity in what may previously have seemed a fairly straightforward question. In the age of chemiluminescent and immunoradiometric GH assays with very low limits of sensitivity, the criteria for biochemical cure are debatable *(9,10)*, but it is important to note that the attainment of biochemical results meeting a strict definition of normal GH secretory dynamics may not be necessary for normalization of acromegaly-associated mortality.

When comparing efficacies of the different treatments of acromegaly, the endocrinologist is faced with inspecting outcomes data often expressed dissimilarly, with many various methods suggested for the assessment of disease status. The biochemical markers that have been used in the postoperative follow-up of patients with acromegaly include basal GH, the mean serum GH from four collections within a day or from eight hourly samples, OGTT-induced GH suppression, and measurement of circulating IGF-1 and/or IGF-BP3. At least some alleviation of symptoms, particularly of arthralgias, can occur with any significant decrease in GH and IGF-1 levels, even though GH secretion may remain abnormal *(11)*. Historically, the most widely accepted indicator of treatment success or failure in terms of morbidity and mortality was the lowest random GH concentration achieved after surgery. Normalization of the mortality rate associated with untreated acromegaly has been demonstrated when a random GH level of <2.5 ng/mL as measured by radioimmunoassay *(12,13)* is achieved, and even when a level <5 ng/mL is reached *(8,14)*. By no means can these cutoffs be construed to necessarily represent normalized GH secretion, however. Two recent studies demonstrate that regardless of treatment modality, when assessed by OGTT-GH suppression and employing a sensitive GH assay, GH secretion remains abnormal in the majority of patients *(15, 16)*, although a window of "safe" GH secretion may be determined. Costa et al. recently *(16)* compared the GH response to OGTT in 56 healthy control subjects with that in 32 patients treated for acromegaly. Based on their analysis, the criterion of glucose-suppressed GH to under 1 ng/mL was advocated as indicative of safe GH secretion, a conclusion that supported previously published recommendations *(17)*.

Measurement of serum IGF-1 concentration affords a depiction of overall 24-h GH secretion or, more precisely, the overall 24-h GH-tissue effect. As such, IGF-1 probably represents the best and most cost-efficient way of assessing the adequacy of surgical and/or medical treatment of acromegaly presently available *(14)*. The lowering of IGF-1 has been associated with reductions in acromegaly-related mortality *(15)*, yet questions surrounding the significance of IGF-1 levels remain to be answered, since normalization of IGF-1 may still be accompanied by persistently abnormal secretory GH dynamics *(15,16,18)*. The clinician must bear in mind that liver disease, nutritional state, age, and sex may alter the GH/IGF-1 relationship.

The Dopamine Receptor Agonists

Dopamine, a catecholamine neurotransmitter with conspicuous actions in the basal ganglia governing motor control, also serves as a neuroendocrine regulator. In the anterior

pituitary, dopamine inhibits the release of prolactin (PRL) and stimulates GH release in healthy subjects, although it paradoxically suppresses GH release in some patients with acromegaly. Dopaminergic D_2 receptors are expressed by some pituitary somatotropes, and approximately one in three GH-secreting pituitary adenomas cosecretes PRL *(19,20)*. Currently available synthetic dopamine agonists—bromocriptine, pergolide, and cabergoline—are derived from ergot alkaloids originating in the fungus *Claviceps purpurea (21)* and have been used in the treatment of acromegaly since bromocriptine first became available in 1974 *(22,23)*. Dopamine agonists are significantly less effective in normalizing the hormonal milieu in acromegaly than they are in hyperprolactinemia, yet the advent of drugs with greater D_2 receptor affinity than bromocriptine has established them as legitimate agents in the medical treatment of GH hypersecretion.

Many of the early efficacy studies of bromocriptine in acromegaly assessed outcome based on percentage of suppression of GH from baseline levels. However, as 24-h GH hypersecretion increases, serum IGF-1 levels increase in parallel until GH reaches a concentration of 10–20 ng/mL, at which point IGF-1 concentrations plateau *(24)*. Therefore, although serum GH concentration may decrease significantly under the influence of a given medication, IGF-1 levels are unaffected if the mean GH concentration remains above 10–20 ng/mL. A 1994 compilation of 31 studies of bromocriptine using daily doses of 5–80 mg and involving a total of 549 patients with acromegaly showed an overall success rate (defined as suppression of GH to <5 ng/mL) of 20%, while IGF-1 was normalized in only 10% of patients *(21)*. Published studies of pergolide are much fewer than those of bromocriptine. Combining the results of two small studies involving a total of 15 patients with acromegaly revealed that pergolide in daily doses of 100–1500 μg over 4–31 mo suppressed GH to an average of approx 50% of baseline, while only 27% (4/15) of patients achieved a serum GH under 5 ng/mL *(25,26)*.

Cabergoline (Dostinex®; Pharmacia, Peapack, NJ) has a prolonged serum half-life in comparison with bromocriptine and is superior to it in the treatment of hyperprolactinemia, with greater tolerability and efficacy. Results of small early studies of cabergoline involving 3–11 patients with acromegaly were contradictory *(27–30)*. However, in the first multicenter trial of cabergoline in 64 patients with acromegaly reported by Abs et al. *(31)*, serum IGF-1 was lowered to <300 ng/mL in 35% (17/48) of patients without concurrent hyperprolactinemia, and in 50% (8/16) of patients with both GH and PRL hypersecretion. Patients with a pretreatment serum IGF-1 of <750 ng/mL had a more robust response. Random serum GH was lowered to less than 2 ng/mL in 46% (30/64) of patients, and to between 2 and 5 ng/mL in another 27% (17/64). The weekly dose of cabergoline was 1.75 mg or less in 87% (56/64) of patients. In a smaller study, Cozzi et al. *(32)* reported the effect of cabergoline in 18 patients with acromegaly over 6 mo of treatment. Mean basal GH decreased from 6.6 ng/mL before treatment to 3.5 ng/mL afterward, while mean IGF-1 decreased from 720 to 375 ng/mL. Serum IGF-1 levels were normalized in 27% (5/18) of the patients. In both studies combined, pituitary adenoma size was reduced in 67% (16/24) patients, and cabergoline was generally well tolerated *(31,32)*. Combining data from all of these studies *(27–32)* revealed that treatment with cabergoline normalized serum IGF-1 in 31.8% (36/113) of patients with acromegaly studied, although IGF-1 was significantly decreased in a greater number.

Although the treatment of acromegaly is an off-label use for cabergoline, it appears to offer the best efficacy of the dopamine agonists in the medical treatment of this disease. In light of its superior side effect profile in comparison with the older dopamine agonists, and its lower cost in comparison with the somatostatin analogs, cabergoline is a legitimate first choice for adjuvant postoperative treatment of persistent GH hypersecretion.

The Somatostatin Analogs

The development of synthetic agents with the property of binding and activating somatostatin receptors placed an important tool in the hands of the endocrinologist treating patients for GH hypersecretion. Since their introduction in the 1980s, somatostatin analogs have been effective in controlling GH oversecretion in a sizable proportion of patients with acromegaly. Still, the precise role these agents will take in the future remains undetermined; a more effective strategy for disease control, GHR blockade, appears to be nearing clinical practice. Somatostatin analogs are frequently very effective in the treatment of acromegaly, though not universally so, as published series demonstrate.

The discovery of a native hypothalamic hormone with GH-suppressing properties was reported in 1968 *(33)*. Because of its inhibitory effect on somatotropin secretion, the hormone was called somatostatin, and was determined to be a cyclic peptide of 14 amino acid length (SS-14). Twelve years later its amino-terminal extended congener, SS-28, was described *(34)*. Somatostatin is a universal suppressor of a multitude of pituitary and extrapituitary hormones and even nonendocrine processes, a fact that helps to explain its ubiquitous distribution and multiple sites of action. It is found in many different tissues (the lymphatic system, gastrointestinal (GI) tract, endocrine pancreas, various areas in the brain, and anterior pituitary) and generally exerts an inhibitory or regulatory influence. In the anterior pituitary, somatostatin inhibits the release of thyroid-stimulating hormone and GH *(35,36)*.

The full variability of actions exerted by somatostatin is made possible by the multiplicity of receptor subtypes and their distribution in target tissues. Five different somatostatin receptor (SSTR) subtypes were identified and characterized in the 1990s *(37–39)*, all of which belong to the

superfamily of receptors featuring the familiar motif of seven-transmembrane-spanning domains. Intracellular postreceptor effects take place via functional connection between the receptor and adenylate cyclase through the guanine nucleotide (G) protein system; other effects distinct from cyclic adenosine monophosphate production have also been demonstrated. Receptor subtypes 2 and 5 (SSTR2 and SSTR5) predominate on the surface of pituitary somatotropes, and somatotrope adenomas may exhibit greater receptor expression than surrounding normal pituitary *(40,41)*. The ratio of SSTR2/SSTR5 mRNA transcripts among GH-producing pituitary adenomas is highly variable *(42)*, and some tumors express neither receptor subtype *(43)*.

The ability of native somatostatin to inhibit GH secretion in vitro and in vivo made it an attractive hormone to explore for primary treatment and postoperative adjunctive treatment of acromegaly, although significant problems in drug delivery stood in the way of clinical use. Somatostatin has a very short elimination half-life of <3 min in serum, a property that would necessitate its delivery by constant iv infusion to achieve stable serum concentrations capable of significant suppression of GH. Furthermore, its rapid decline in serum was followed by rebound hypersecretion of GH, insulin, and glucagon *(44)*. The need for development of an exogenous ligand with a longer half-life, capable of binding and activating SSTR2 and SSTR5, was clear.

These difficulties in somatostatin pharmacokinetics and drug delivery were overcome with the development of the synthetic SSTR2-directed somatostatin analogs, octreotide (Sandostatin®; Novartis, East Hanover, NJ) and lanreotide (Somatuline®; Ipsen, Maidenhead, Berkshire, UK). Only octreotide is available for clinical use in the United States. Octreotide suppresses GH secretion 45 times more potently than native SST-14 *(45)*, and with a half-life after sc injection of 90 min, it can be self-administered three times per day. It is usually given in doses of 300–750 μg daily, divided into three injections, but up to 1500 μg can be given daily when necessary for control of symptoms. GH secretion is rapidly suppressed after a single sc injection of octreotide, with a maximal effect between 2 and 6 h after injection *(46)*.

Limited, initial studies of octreotide therapy in acromegaly were encouraging *(47–50)*, and in a multicenter trial involving 189 patients with acromegaly followed from 1 to 33 wk on octreotide, serum GH was reduced to <5 ng/mL in 45% *(51)*. This was a heterogeneous group of patients, of whom 75% received octreotide as secondary therapy (the largest single group had undergone surgery and had had unsatisfactory responses to bromocriptine and pituitary irradiation as adjunctive therapies). Octreotide was also reported to decrease macroadenoma tumor volume by about 75% in one case report *(52)* and by 20–54% when given preoperatively in a small group of patients *(53)*. The effect of octreotide on tumor size is reportedly owing to a direct reduction in cell volume or number, as opposed to an effect on tumor vascular supply *(54)*.

The potential problem of poor compliance with a regimen of three daily injections provoked the development of slow-release formulations of octreotide and lanreotide. The active drugs were encapsulated within slowly dissolving biodegradable polymer microspherules that allowed the gradual release of drug over about 30 days after depot injection *(55)*. Within an hour after a single im injection of long-acting release (LAR) octreotide (Sandostatin LAR®), serum octreotide levels rise very briefly as the drug coating the surface of the microspherules enters the circulation. After a rapid fall, the serum concentration then rises again between 7 and 14 days after injection, and remains at a plateau for another approx 19 d, before gradually tapering off *(56)*. The duration of effect, but not the potency of GH suppression, is augmented by increasing doses. Monthly (every 4 wk) im injections allow for octreotide levels sufficient for constant GH suppression to be maintained, although adequate control may also be maintained on an every 6-wk injection regimen in some patients *(57)*.

The slow release (SR) form of lanreotide is also achieved through the use of biodegradable microspherules containing active drug and given as a depot injection. The shorter serum half-life of lanreotide SR in comparison with octreotide LAR necessitates its injection frequency of 10–14 d *(58)*. A newer galenic form of lanreotide, a deep sc administered gel preparation, has recently been introduced in clinical studies and has the potential of offering monthly injections *(59)*. Lanreotide is available for use in Europe.

A significant decrease in serum GH and IGF-1 levels is seen in most patients with acromegaly treated with long-acting somatostatin analogs, but only about half of patients may be expected to achieve enduring, normalized GH profiles. In a recent review summarizing published outcomes, Freda *(60)* reported that GH levels were suppressed in an average of 56% of patients treated with octreotide LAR (compiling data from 7 studies), and in an average of 49% of patients treated with lanreotide SR (in 12 studies). Wide variability in outcomes is reported and may be owing to differences in length of follow-up, drug doses, and criteria employed in the assessment of GH status. Serum levels of IGF-1 were lowered to the normal range in an average of 66% of patients treated with octreotide LAR (in 6 combined studies), and in an average of 48% of patients treated with lanreotide SR (in 13 studies). As observed by Freda *(60)*, most studies examining the efficacy of octreotide LAR analyzed response to treatment in patients already determined to respond to sc octreotide, and, therefore, the data on LAR therapy may not accurately predict response rates in unselected patients. Only a minority of patients studied who were taking lanreotide SR therapy were preselected for response to sc lanreotide.

The reported efficacy of somatostatin analogs in reducing tumor volume was also assessed in the review by Freda *(60)*. Data from 15 studies of either long-acting preparations or sc octreotide were gathered, yielding a rate of tumor shrink-

age of about 30%, with most studies reporting a decrease in tumor volume of between 20 and 50% *(60)*.

Somatostatin analogs have a beneficial effect on cardiac performance in patients with acromegaly. Colao et al. *(61)* examined the effects of sc octreotide on left ventricular ejection fraction (LVEF), heart rate, blood pressure, exercise duration, and exercise workload in 30 patients with acromegaly, 13 of whom had normalized GH (defined as basal GH < 2.5 ng/mL or OGTT-suppressed GH < 1 ng/mL) and normalized age-matched IGF-1 after 1 yr of treatment. In these 13 patients, LVEF at both rest and exercise improved significantly, increasing from 56.5 to 66.5% at rest, and from 52.6 to 67.1% after exercise. Resting and exercising heart rate were decreased, and exercise duration and workload were significantly increased in this group whose biochemical parameters were normalized. Conversely, in the 17 patients with persistently elevated serum GH and/or IGF-1 concentrations, resting LVEF did not change at 12 mo, but LVEF at exercise was significantly decreased as compared with the resting value, from 64.9 to 57.2%, while average resting systolic blood pressure increased in this group from 128.5 to 141.2 mmHg. In a similar study of octreotide LAR in 15 octreotide-naïve patients, left ventricular mass index (LVMi), interventricular septum thickness, and LV posterior wall thickness were improved in all patients after 3 and 6 mo of treatment *(62)*. Six of 11 (55%) patients with left ventricular hypertrophy at study entry normalized their LVMi while on treatment. These positive cardiovascular effects of octreotide are generally seen to occur more slowly in older patients with longer disease duration *(62)*.

Because of the wide distribution and varied functions of SSTRs, the use of SST analogs may be accompanied by significant side effects, most of which are related to the GI tract. In a report of 103 patients treated with sc octreotide, Newman et al. *(63)* reported side effects including diarrhea, nausea, abdominal discomfort, and loosened stools, but these usually resolved within 3 months of treatment. The formation of gallbladder sludge occurred in 20.6% of 102 patients with normal ultrasound examinations at baseline, and another 23.5% developed gallstones. No patient developed cholecystitis.

Octreotide may alter carbohydrate metabolism because of its effect on insulin and glucagon secretion, although these concerns seem to be of minor consequence in limited follow-up studies of patients. Carbohydrate metabolism was examined in 36 patients followed for up to 24 mo while undergoing octreotide LAR therapy *(64)*. A decrease in fasting serum insulin levels (10.5 mU/L on treatment vs 17.7 mU/L before) was observed to follow a small but significant increase in fasting serum glucose levels (95 mg/dL on treatment vs 106 mg/dL before) after 3 mo of treatment, but no difference was found in serum glucose concentrations after 12–24 mo of treatment. Whether longer-term treatment with somatostatin analogs increases the risk of developing type 2 diabetes mellitus is not known, and, therefore, careful yearly follow-up of fasting and perhaps postprandial glucose levels seems a sensible precaution.

Long-acting formulations of the somatostatin analogs serve a prominent role in the treatment of acromegaly after unsuccessful adenomectomy, and they may also be useful as primary therapy (see review, Somatostatin Analogs as Primary Medical Therapy for Acromegaly, pp. 291–297). Their major benefits over subcutaneously injected somatostatin analogs stem from greater ease of compliance with once or twice monthly injections, as opposed to thrice daily injections. The improved cardiovascular profiles in patients treated with somatostatin analogs who achieve normalized GH and/or IGF-1 are in keeping with the normalized mortality shown previously by retrospective survival data of "cured" acromegaly (random GH < 2.5 ng/mL). Response rates of patients treated with these agents as adjunctive medical treatment following surgery are in the range of 50–70%, whether assessed by IGF-1 or GH normalization. Although these rates signify a clear improvement over the dopamine agonists, a substantial percentage of patients do not benefit satisfactorily. These patients may eventually be helped more from other treatments on the horizon; somatostatin analogs featuring broader SSTR-binding profiles and potentially higher effectiveness for GH suppression are being developed and may contribute further efficacy in the treatment of acromegaly *(65)*.

GHR Antagonist Therapy

The third strategy for medical control of disease status in patients with acromegaly hinges on a mechanism fundamentally distinct from the suppression of serum GH levels, being based instead on a principle of disruption of interaction between GH and end-organ tissue. This strategy carries an advantage over somatostatin analogs and dopaminergic agents in that it is independent of tumor expression of somatostatin or D_2 receptors. Blockade of the physiologic action of GH at the cellular level occurs through the use of a modified GH molecule, a competitive antagonist of the GHR. This therapy appears promising in two published studies examining its efficacy and safety and represents a substantial advancement in the medical treatment of acromegaly. Pegvisomant (Somavert®; Pharmacia), the pioneer compound aimed at treating acromegaly under this paradigm, may reach the market in early 2003.

The design of a GHR antagonist was cleverly pursued following elucidation of the mechanism of interaction between GH and its receptor. Human GH is a 22-kDa, 191 amino acid polypeptide chain with a secondary structure of four α-helices in a bundled core. Each GH molecule presents two separate binding domains (sites I and II) for the interface with two GHRs and is, therefore, a bivalent molecule capable of inducing the dimerization of two GHR molecules. The GHR is made up of intracellular and extracellular domains, linked by a transmembrane component. In serum, 40–50% of GH is bound by GH-binding protein *(66)*, which

is identical to the extracellular domain of GHR *(67)*. As freely circulating GH comes into contact with a single GHR molecule on the cell surface, it is bound at binding site I and forms the GH-GHR complex. The GH-GHR complex then undergoes a conformational change that allows the subsequent binding of a second cell-surface GHR molecule *(68–70)*. The dimerization of GHRs is the final necessary event for activation of signal transduction, and transcription of the genes coding for IGF-1 follows sequentially.

Pegvisomant is an analog of GH with nine genetically engineered amino acid substitutions within binding sites I and II that result in two important deviations from the action of wild-type GH. First, pegvisomant is given a kinetic advantage over native GH by virtue of the 30-fold increased affinity of its binding site I for GHR *(71,72)*. Second, after the binding at site I of the pegvisomant molecule with GHR, the binding of a second GHR is prevented by the presence of a substituted amino acid in site II with a long side chain. Thereby the dimerization of GHRs is not permitted, and signal transduction is prevented *(73)*. The competitive advantage of pegvisomant over native GH is further enhanced by the addition of four to five polyethylene glycol moieties, which results in a prolonged serum half-life of nearly 3 d, and lowers immunogenic potential *(74,75)*. For an excellent overview of the physiology of GH-GHR interaction and of the design of pegvisomant, the reader is referred to the 1999 review by Parkinson and Trainer *(76)*.

In the first published trial of a GHR antagonist in the postoperative treatment of acromegaly *(77)*, Trainer and a multicenter group of investigators administered pegvisomant or placebo in daily sc injections to 112 patients over a 12-wk period. Patients were randomized to receive pegvisomant in doses of 10, 15, or 20 mg, or placebo. Pegvisomant given in a daily dose of 20 mg resulted in normalization of serum IGF-1 in 89% of patients, whereas the 15- and 10-mg dose groups achieved normalized IGF-1 in 81 and 54%, respectively. Symptom complexes including fatigue, excessive perspiration, and soft-tissue swelling as assessed by ring size were followed, and significant improvement of these occurred in patients treated with 15 and 20 mg of pegvisomant daily. In a larger follow-up study by van der Lely et al. *(78)*, 160 patients were treated with pegvisomant in doses up to 40 mg daily, for an average follow-up of almost 14 mo. Serum IGF-1 reverted to normal in 97% (87/90) of patients treated for 12 mo or more. In an observation that reflects the insulin resistance and hyperinsulinemia of acromegaly, fasting serum insulin during treatment fell from 23 to 15.8 mU/L at 6 mo of follow-up, while fasting serum glucose fell from 105 to 86 mg/dL. Glycated hemoglobin concentrations did not change.

When the data from both studies were taken together, it was found that antibodies to pegvisomant and to GH were detected in 16.9 and 8.8% of patients, respectively, though no patient showed evidence of tachyphylaxis. Pegvisomant was well tolerated in both studies; however, new serologic evidence of asymptomatic hepatocellular injury without hepatobiliary involvement was noted in three patients (1.1%) shortly after the initiation of pegvisomant. Aminotransaminase levels returned to normal in all three patients when the drug was withdrawn. In light of this uncommon side effect, careful monitoring of liver transaminases during the first few months of treatment will be necessary. Serum GH concentrations increase during pegvisomant therapy, probably a result of the loss of negative feedback owing to the lowering of serum IGF-1 concentrations. Because of decreased negative feedback, there is a theoretical risk of enlargement of the pituitary adenoma while undergoing GHR antagonist treatment, a prospect that deserves careful attention. In the two studies just summarized, patients were examined with pituitary magnetic resonance imaging (MRI) before and after treatment with pegvisomant. Two patients had enlargement of their tumors during therapy, but one may have enlarged during a 5-month period on octreotide alone, and both tumors appeared to be aggressive independent of treatment. A later subanalysis of MRI data from 131 patients in the study by van der Lely et al. *(78)* accounted for tumor volume before and after pegvisomant and stratified tumor response according to prior treatment scheme *(79)*. Mean tumor volume at baseline was 2.38 cm^3 (range: 0.11–15.18) and decreased by 0.04 ± 0.06 cm^3 after a mean follow-up of 53 wk. None of the prior-treatment groups showed a significant change in tumor volume in relation to baseline, nor in relation to other treatment groups. Because some small percentage of somatotrope adenomas normally exhibit aggressive behavior and growth, this rate of tumor enlargement, 0.8%, is less than the rate of tumor growth (about 7%) in a recently published study of patients with acromegaly treated preoperatively with octreotide *(80)* and may not be related to pegvisomant treatment.

GHR antagonist therapy appears to offer the promise of a very high rate of normalization of IGF-1 in patients with acromegaly not adequately treated by any combination of surgery, radiation, and/or GH suppression therapy. The added dimension of medical management afforded by pegvisomant, by nature of the prevention of postreceptor signal transduction, is a novel modality and is exemplary of the clinical application of genetic engineering. The uncommon but potentially threatening liver enzyme elevation indicates the need for caution in the use of pegvisomant in patients with known liver disease, and monitoring of liver markers should be standard practice for all patients treated, although the duration of surveillance necessary remains to be determined. The serum IGF-1 of a patient on pegvisomant should be maintained within the normal age- and sex-adjusted range to avoid symptoms of GH deficiency. Safety and efficacy studies of pegvisomant in children with gigantism, in pregnant women, and as primary therapy for the treatment of acromegaly are needed. Pegvisomant may prove very useful as primary therapy in those patients who are unwilling or unable to undergo transsphenoidal surgery.

Table 1
Comparison of Medical Treatment Strategies in Acromegaly

Therapy	Normalization of IGF-1	Advantages	Disadvantages
Dopamine agonists	Cabergoline: 32% Bromocriptine: 10%	Oral administration Relatively inexpensive Generally well-tolerated	Ineffective in majority Numerous side effects, though generally mild
Somatostatin analogs	Octreotide LAR: 66% Lanreotide SR: 48%	Every 2–4 wk depot injection Enhanced efficacy compared to dopamine agonists Tumor shrinkage in 20–50%	Costly Ineffective in nearly half Numerous potential side effects, though generally well tolerated
GHR antagonist (pegvisomant)	20 mg/d: 89% 40 mg/d: 97%	Independent of somatostatin/D2 receptors Extremely effective in inducing biochemical control	Daily sc injection Expected to be costly ? Tumor growth ? Liver enzyme elevation

Conclusion

The majority of patients with acromegaly require further treatment for disease management following pituitary microsurgery. The benefits of radiotherapy, in terms of subdued GH hypersecretion, require several years to materialize, while the regrettable side effect of hypopituitarism occurs in about half of patients within 10 yr. Meanwhile, the armamentarium available for the medical treatment of acromegaly has developed into an adaptable assortment of therapies from which to choose, and still more formulations are expected to appear. The advantages and disadvantages of the three pharmacologic approaches to acromegaly are summarized in Table 1. GH suppression with cabergoline is well tolerated and remains a viable treatment strategy, although only about one-third of patients achieve a normalized IGF-1 while taking cabergoline. The depot injectable long-acting somatostatin analogs lanreotide SR and octreotide LAR have become the reference drugs of the medical treatment of acromegaly as a result of their superior efficacy in comparison with the dopamine agonists. Still, not more than two-thirds of cases of persistent acromegaly respond satisfactorily to these agents.

Endocrinologists will soon have available to them the alternative of pharmacologic blockade of the GHR, which will render clinically inconsequential the GH hypersecretion of residual tumor cells refractory to GH-suppressive therapy. Studies of pegvisomant efficacy have underscored the recognition that serum IGF-1 concentration is a more useful marker of disease status in acromegaly than is serum GH. The normalization of IGF-1 should be the foremost biochemical goal of the medical treatment of acromegaly, whether in the setting of GH-suppressive therapy or GHR blockade. This is a point worthy of emphasis, as we embark on an era in which it will be possible to normalize IGF-1 in virtually all patients with persistent acromegaly following surgery.

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