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REVIEW

# An update on the treatment of acromegaly



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**Abstract:** Acromegaly is caused by pituitary somatotroph hypersecretion of growth hormone leading to elevated hepatic-derived and local levels of insulin-like growth factor-1. It is associated with increased morbidity and mortality due primarily to cardiovascular disease and diabetes mellitus. Normalization of growth hormone and insulin-like growth factor-1 levels has been associated with decreased morbidity from metabolic and cardiovascular effects, as well as reduced overall mortality in epidemiologic studies. Many patients experience a delay in obtaining a diagnosis, have pituitary macroadenomas at presentation, and accordingly, a significant number will not be cured by tumor surgical resection alone. Adjunctive radiation therapy cannot always offer biochemical and clinical disease control and carries a 40% risk of partial or total pituitary failure in the medium term. Several monotherapies or combination medical therapies are currently available for both primary and adjuvant acromegaly treatment, and include long-acting somatostatin analogs, the growth hormone receptor antagonist pegvisomant, and dopamine agonists. Next generation somatostatin analogs and new drug delivery methods of existing agents are in ongoing clinical studies. This paper will review current and novel therapies under development for acromegaly.

**Keywords:** acromegaly, growth hormone, pituitary tumors, somatostatin analog, pasireotide, pegvisomant

## Background

Acromegaly is characterized by the hypersecretion of growth hormone (GH). Secretion of GH is stimulated by GH releasing hormone and ghrelin, which is released in the gastrointestinal tract in response to adequate nutrition and is thought to act via the hypothalamus in a similar mechanism to GH releasing hormone. GH secretion is inhibited by somatostatin, which is produced by pancreatic neuroendocrine cells.[1] GH induces the peripheral synthesis of insulin-like growth factor-1 (IGF-1), primarily by the liver, although some is locally generated. There is evidence that GH and IGF-1 have independent functions, particularly in normal growth and development. Notably, GH and IGF-1 tend to have opposite effects upon metabolic parameters such as insulin resistance.[2] As counterregulatory hormones, GH and IGF-1 are closely linked to glycemic status. The hypersecretion of these hormones induces systemic effects, visceromegaly, cardiomyopathy, and soft tissue enlargement.[1]

The annual incidence of acromegaly has traditionally been reported at three to four cases per million, with a prevalence of 40–125 cases per million.[3] However, more recent studies have proposed that the incidence may be as high as 1043 cases per million.[4] The signs and symptoms of acromegaly are often subtle, and many patients have had

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the disease for 7–10 years prior to definitive diagnosis.[5] Over 90% of cases are caused by a benign pituitary adenoma comprised of somatotrophs,[6] and more than 70% of these pituitary tumors are macroadenomas (>1 cm in diameter) at the time of diagnosis.[7]

## Definition of disease control

### Biochemical control

Uncontrolled acromegaly carries a 2- to 2.5-fold increase in mortality, due primarily to cardiovascular disease and complications of diabetes. Normalization of GH and IGF-1 has been shown to return mortality to that of the general population in a surgical series.[8] In treated acromegalic patients, acceptable values for random GH levels have evolved, ranging from <2.5 ng/mL on older assays to <1 ng/mL on newer assays. The 2010 Acromegaly Consensus Group established a more stringent definition of disease control, defined as an IGF-1 level in the age-adjusted normal range and a random GH level < 1 ng/mL. Several studies in the postsurgical patient suggest that a GH level < 0.4 ng/mL during a 75 g oral glucose tolerance test (OGTT) 3–6 months following treatment may be used to define disease control,[9] but no additional benefit of obtaining an OGTT in patients on somatostatin analogs has been observed.[10] These evolving criteria raise important caveats for clinicians to consider. Firstly, older clinical trials completed prior to the adoption of these new criteria using random GH levels < 2.5 ng/mL or even <5 ng/mL to define disease control need to be interpreted with some limitations. Secondly, given its mode of action, GH levels are not a useful indication of disease control in patients treated with the GH receptor antagonist pegvisomant, and here, IGF-1 levels are the sole reliable criteria. Thirdly, it is increasingly recognized that discordance between GH and IGF-1 levels can occur, whereby one marker indicates disease control but the other does not.

This latter finding of discordance has been noted in up to 9.4%–39% of cases, and proposed mechanisms include dysregulation of GH pulses and/or secretion. Other studies have suggested that polymorphisms of exon-3 of the GH receptor could impact disease severity.[11,12] Although prior studies had suggested discordance was a feature of patients previously treated with somatostatin analogs or radiation therapy, a recent study has described this phenomenon in treatment-naïve patients.[13] This group of patients is of interest as it has been suggested that an elevated IGF-1 in the setting of a normal GH level may have more detrimental effects upon glucose metabolism than an elevated GH associated with normal IGF-1 levels.[14] In some cases of IGF-1 and GH discordance, frequent GH sampling (every 15 minutes for 2 hours) may help determine if an acromegalic patient is controlled.[9] Clinical management decisions must be made on an individual basis taking into account both IGF-1 and GH levels, as well as comorbid conditions and their relation to quality of life.

Another area of discussion pertains to the timing of biochemical evaluation after therapy. Although hormone measurements at 3–6 months are considered to be more reliable at predicting long-term disease control, several smaller studies have suggested that GH levels and OGTT may have some predictive value in the immediate postoperative period.[15,16] A recent large study of 194 patients found that a 24-hour postoperative random GH level < 1 μg/L was associated with the highest probability of remission (98%). The 1-week OGTT was 81.7% sensitive and 95.1% specific for remission, while the 6-month OGTT was 92.2% sensitive and 88.9% specific.[17] Although an abnormal postoperative finding would not obviate the need for repeat testing several weeks later, it may identify patients who could benefit from earlier initiation of adjuvant therapy.

### Tumor control

In addition to biochemical control, given the proximity of the pituitary gland to critical structures such as the optic chiasm, cranial nerves, and vascular structures including the internal carotid arteries and the cavernous sinus, control of tumor growth is important. Clearly, surgical resection has the ability to offer immediate tumor control, whereas radiation and medical therapy will take much longer. Unlike biochemical parameters (IGF-1 and GH), no tight correlation with morbidity or mortality and tumor volume exists. There is no consensus regarding the definition of "clinically significant" tumor shrinkage in first-line or adjuvant medical therapy, but recent studies have used reductions ranging from 10%–45%. A recent analysis suggests that tumor shrinkage may be greater in patients receiving first-line treatment with somatostatin analogs.[18] Based upon varying definitions of tumor volume reduction, tumor control is possible in approximately 34%–38% of somatostatin analog-treated patients and 5% of dopamine agonist-treated patients.[19] A recent metaanalysis of 41studies suggested that a 20% reduction in tumor volume or diameter is clinically significant in the setting of both adjuvant or primary therapy, and that 57% of patients treated with octreotide long-acting release (LAR) achieved tumor control based upon this definition.[20] In contrast, given its mode of action, pegvisomant will either have a neutral effect on pituitary tumor growth or, as reported in occasional patients, be associated with tumor growth.

# Currently available therapies

## Surgery

Primary surgical intervention is considered the preferred treatment for acromegaly, and has two main goals: biochemical remission and protection of threatened anatomic structures such as the optic chiasm. The majority of studies prior to the 2009 consensus criteria defined disease control as a normalized age- and sex-matched IGF-1, glucose-suppressed GH < 1 ng/mL,[21–23] and remission rates ranging from 42%–72%. Surgical cure was obtained in 67%–95% of microadenomas, but only 47%–68% of macroadenomas.[24] More recent studies based upon updated criteria (normalized age- and sex-matched IGF-1, glucose-suppressed GH < 0.4 ng/mL on sensitive assays) demonstrated comparable results.[9,25] In a study of 60 acromegalic patients undergoing endoscopic endonasal transsphenoidal surgery, the overall remission rate was 70%, with remission achieved in 100% of microadenomas and 61% of macroadenomas.[24] The challenge of attaining surgical remission in macroadenomas is further emphasized in a similar study of 24 patients undergoing endoscopic endonasal transsphenoidal surgery where 83% were macroadenomas. Gross total resection was achieved in only 71% and resulted in a 45% remission rate.[26]

Surgical debulking may also have a role as second-line or adjuvant therapy in patients with unresectable tumors who are uncontrolled by primary treatment with somatostatin analogs. Two studies compared biochemical control rates with somatostatin analog therapy before and after debulking pituitary surgery. First-line somatostatin analog therapy resulted in the control of GH and IGF-1 in 14%–29% and 10%–45% of patients preoperatively compared to 54%–56% and 55%–78% following debulking surgery, respectively.[27,28]

## Radiation

Radiation therapy is typically recommended in patients with uncontrolled acromegaly who have failed surgical and/or several medical therapies. The major drawbacks to radiation treatment are the time delay from treatment administration to disease remission and the likelihood of hypopituitarism. Because the decline in GH levels is gradual, the time to remission correlates with the initial GH level. A recent metaanalysis of twelve studies evaluating fractionated radiation therapy in 1128 patients reported tumor growth control in 80%–90% and normalization of GH and IGF-1 in 50%–60% of patients at 10 years. The rate of hypopituitarism over the same time period was 60%.[29] This metaanalysis also examined stereotactic radiosurgery (including gamma knife® radiosurgery; Elekta AB, Stockholm, Sweden) in 16 studies of 935 patients. Tumor growth and biochemical control was obtained in 88%–97% and 30%–60% of patients at 5 years, respectively, which was comparable to the fractionated studies. Rates of hypopituitarism were also similar at 20%–40% over 5 years.[29] When reviewing studies since 2003 only, the overall biochemical remission rates for Gamma Knife radiosurgery range from 17%–53%.[30] One area of controversy relates to the potential for decreased efficacy of radiation therapy in the setting of concurrent somatostatin analog therapy. Some studies have reported that somatostatin analogs may be radioprotective and thus impair radiation efficacy;[31,32] however, data are conflicting and no current guidelines regarding withdrawal of somatostatin analog therapy exist.

## Medical therapy: monotherapy

### Somatostatin analogs

Over 90% of somatotroph (GH-secreting) adenomas express somatostatin receptor subtype-2 (SSTR2) and SSTR5,[1] to which currently approved somatostatin analogs selectively bind. Long-acting preparations of both octreotide and lanreotide are available. Octreotide LAR is given intramuscularly every 4 weeks, lanreotide sustained release (SR) is given intramuscularly every 7–14 days (not available in the US), and lanreotide autogel (ATG) is given by deep subcutaneous injection every 4, 6, or 8 weeks. Somatostatin analogs exert their maximum effect on GH levels after 3–6 months,[33] and on IGF-1 levels by 6–12 months.[34]

Attempts have been made to identify patients who will exhibit a good response to somatostatin analogs. For example, it has previously been demonstrated that so-called "densely granulated" somatotroph adenomas are more likely to respond to somatostatin analogs than sparsely granulated adenomas, with long-term IGF-1 normalization rates of 52% versus 7%, respectively.[35] The determination of granulation, of course, requires histopathologic examination of sugically resected specimens, and will not therefore assist evaluation of somatostatin analogs in a primary medical therapy setting. A recent study of 45 newly diagnosed acromegalic patients evaluated the predictive value of magnetic resonance imaging (MRI) findings. The tumors were classified as hyperintense, isointense, or hypointense on T2 imaging at the time of diagnosis, and 34 patients went on to have a histopathologic diagnosis. T2 hyperintensity on MRI correlated closely with a sparse granulation pattern on pathology, and these both predicted a poor response to somatostatin analogs based upon percent reduction in IGF-1 and GH levels after

6 months of treatment.[36] This preliminary report suggests MRI appearance may have the potential to help predict response to somatostatin analog therapy, although further investigation is needed to determine the practical application of this approach.

## Somatostatin analog monotherapy

### Neoadjuvant therapy

Several recent studies have evaluated the use of octreotide LAR for 3–6 months in newly diagnosed, untreated acromegalic patients prior to surgical intervention. Two prospective, randomized studies reported significant decreases in tumor size of 35%–37% with preoperative somatostatin analog therapy, although a third prospective study found no significant change in tumor size. Short-term remission rates based upon normalized IGF-1 and OGTT GH $<$ 1 ng/mL obtained in the first 3–6 months postoperatively appeared to increase with neoadjuvant somatostatin analog treatment compared to surgery alone (24%–42% versus 10%–23%), although long-term remission rates were unaltered.[37–39]

### Primary therapy

Primary therapy with somatostatin analogs may achieve biochemical remission in a significant subset of patients. In one prospective study, primary octreotide LAR treatment resulted in normalization of IGF-1 and GH $<$ 2.5 μg/L in 34% and 44% of subjects, respectively, as well as inducing significant tumor shrinkage (>20%) in 75% of patients.[40] This biochemical response was less robust than the reported rates of approximately 60% in two other large studies using similar criteria for biochemical cure.[41,42] The majority of patients had macroadenomas, but all three studies indicated that patients with smaller tumors and lower initial IGF-1 levels tended to have higher response rates. A direct prospective comparison of lanreotide SR and octreotide LAR in 20 treatment-naïve patients showed achievement of biochemical control in 70% of microadenomas and 10% of macroadenomas, as well as a 28% reduction in tumor volume, and found no difference in the effectiveness of either medication.[43] A large retrospective study of the German Acromegaly Register compared primary therapy with somatostatin analogs (145 patients) to surgical resection (554 patients). GH and IGF-1 normalized in 54.3% and 67.2% of surgical patients compared to 40.8% and 41.5% of patients treated with somatostatin analogs for at least 1 year.[44] The latter study supports the place of surgery as the mainstay of treatment in acromegaly; however, primary therapy with somatostatin analogs is a viable option for patients who are poor surgical candidates, have unresectable tumors, or decline surgery.

### Adjuvant (postsurgical) therapy

Until comparatively recently, the main role of somatostatin analog therapy was in the postsurgical setting in patients not exhibiting clinical and/or biochemical remission. Hence, there are many studies evaluating somatostatin analog therapy in this group of patients, many of which attempt to determine which somatostatin analog is most effective. For example, an analysis of 44 studies involving 1852 patients comparing lanreotide SR and octreotide LAR suggested improved biochemical control with octreotide LAR based upon GH and IGF-1 criteria, respectively (octreotide LAR 57% and 67%, lanreotide SR 48% and 47%).[33] However, the GH criteria chosen to determine remission in the analyzed studies were quite variable, making a clear comparison difficult. Several small, open studies that directly compared these two agents have suggested that octreotide LAR may be slightly more effective than lanreotide SR for biochemical control, although these studies have several limitations including the crossover study design in which patients were initially treated with lanreotide SR.[45]

Overall, no significant difference between the effectiveness of lanreotide ATG and octreotide LAR has been substantiated. The largest study to date comparing octreotide LAR and lanreotide ATG in 68 patients found no significant difference in biochemical control defined as a fasting GH $<$ 2.5 μg/L, GH $<$ 1.0 μg/L following OGTT, and normal age- and sex-matched IGF-1 levels (octreotide LAR 64% and lanreotide ATG 78%). Likewise, percent tumor shrinkage was comparable (octreotide LAR 29% and lanreotide ATG 35%). Interestingly, using the OGTT GH cutoff of $<$0.4 μg/L, biochemical control with either agent decreased substantially to 27% for octreotide LAR and 31% for lanreotide ATG.[34] Notably, there was no crossover between drugs in this study, and patients who required additional therapy including a second surgery within 18 months were excluded from the final analysis.

## Long-term somatostatin analog therapy: is withdrawal of therapy possible?

Both for patient convenience and cost considerations, the dosing interval for octreotide LAR and lanreotide ATG can be extended to 6, 8, or even 10 weeks in select patients.[46,47] Furthermore, recent studies have suggested that prolonged use of somatostatin analogs results in reduced quality of life, regardless of IGF-1 levels, emphasizing the impor-

tance of this question.[48] A recent study attempted cessation of somatostatin analog treatment in well-controlled patients on extended-interval dosing, analogous to discontinuing dopamine agonists in prolactinoma patients. Patients were considered eligible for withdrawal of somatostatin analogs based upon the following criteria: treated with somatostatin analogs for at least 2 years with a stable dose for 1 year, random GH < 1.5 ng/mL, IGF-1 < 1.2 times the upper limit of age- and sex-matched normal range, and tumor remnant of 8 mm or less on MRI examination. One year after cessation of therapy, 41% of this patient population remained in remission, and it appeared that longer intervals between dosing (10–12 weeks) correlated with an increased likelihood of sustained remission.[49] However, the overall percentage of patients who were able to successfully discontinue therapy was exceedingly small (<3%), and other studies examining this question have observed even higher relapse rates using less stringent GH level criteria.[50] At this time, withdrawal of somatostatin analog therapy is not the standard of practice in either the US or Europe. Based upon the currently available evidence, somatostatin analog therapy in acromegaly should be continued indefinitely.

## Somatostatin analogs: metabolic and cardiac effects

Pancreatic alpha and beta cells exhibit abundant SSTR2 and SSTR5 expression. Native somatostatin is typically low in the fasting state and increased in the fed state. In the setting of hyperglycemia, insulin stimulates somatostatin release, which in turn inhibits further insulin secretion. Somatostatin also inhibits the release of glucagon, largely in the fasting state.[51] Excess GH increases glucose production from the liver via lipolysis and inhibition of suppression of gluconeogenesis by insulin, which can lead to type II diabetes mellitus.[52] Somatostatin analogs increase insulin sensitivity, but also decrease secretion of glucagon and insulin,[53] and as might be expected, they exhibit important effects upon glucose metabolism.

A metaanalysis of 619 acromegalic patients treated with somatostatin analogs for 3 weeks to 96 months at standard doses reported no effect upon hemoglobin $A_{1c}$ or fasting glucose levels, but did observe a worsening response to OGTT. Lanreotide appeared to have a greater impact upon the OGTT response than octreotide, and adverse effects on glucose metabolism were more prominent within the first several months of therapy.[52] A recent study of primary treatment with lanreotide ATG concurred with this metaanalysis, and reported deterioration of glucose control based upon fasting blood glucose and OGTT in 17%, improvement in 24%, and no change in 60% of patients.[54]

Approximately 50% of patients with acromegaly have mortality attributable to cardiovascular disease.[55] Restoring GH to "safe" levels (random GH < 2.5 ng/mL) has been associated with a return of mortality rates to near that of the general population.[56] A recent metaanalysis found several cardiac benefits such as reduced heart rate, decreased left ventricular mass, and improved exercise tolerance following somatostatin analog therapy, although no improvement in hypertension or ejection fraction was seen.[57] Greater decreases in GH and IGF-1 were associated with greater improvement in cardiac parameters, although the level of biochemical control was not known in many studies.[52] It has been proposed that primary or postsurgical somatostatin analog therapy has beneficial cardiovascular effects independent of disease control, which may be attributable to direct effects upon cardiac cells;[55] however, further prospective studies are needed.

## Pegvisomant

Pegvisomant, a GH receptor antagonist, is given subcutaneously and has been used in the US since 2003 and in Europe since 2004. This treatment lowers IGF-1, but due to its mode of action increases GH levels, and thus, IGF-1 levels are the only accurate monitoring modality. Initial studies with daily pegvisomant monotherapy reported normalization of IGF-1 in 89%–97% of cases.[58,59] In a recently published European study using the ACROSTUDY™ database (Pfizer, Inc, New York, NY, USA), which represents a large series of 1288 patients in real-life clinical practice, 88% of patients were receiving daily pegvisomant alone, while 36% were also on other treatments including somatostatin analogs. On an average dose of 18 mg/day, 63% of patients had a normal IGF-1 after 5 years.[60] However, it must be acknowledged that this study may be somewhat limited by several factors, including issues with dose titration and a selection bias for severe disease, as pegvisomant is only approved in Europe for disease uncontrolled by other treatment modalities. Smaller studies with more optimal dose titration have reported higher rates of biochemical control, ranging from 84%–88%.[61,62] Given its half-life of >70 hours, several studies have also examined the feasibility of less frequent dosing, which could improve patient compliance and reduce costs. Alternate-day, twice-weekly, or once-weekly dosing intervals have been demonstrated to effectively maintain normal age- and sex-matched IGF-1 levels in select patients in small studies.[63,64] Several factors which may be associated with response to

pegvisomant therapy have been identified. Female gender and increased body weight have been associated with a higher dose requirement, and prior radiation therapy is associated with a lower dose requirement in order to achieve equivalent biochemical control.[65] A decrease in the necessary dose of pegvisomant has also been associated with the deletion of exon-3 in the GH receptor.[66,67]

Because pegvisomant acts peripherally on GH receptors, it does not have antitumor growth properties, which is in contrast to somatostatin analogs. In ACROSTUDY, a clinically significant increase in tumor size, defined as an increase in diameter by 3 mm or an increase in volume by 20%, was noted in 3.2% of patients,[60] which was comparable to reports in initial clinical trials. Proposed characteristics which may be related to increased risk of tumor growth include higher tumor GH and insulin receptor expression, shorter duration of prior treatment with somatostatin analogs, and lack of prior treatment with radiation.[68] The small but real risk of tumor growth reaffirms the need to carefully select patients without large tumors close to the optic tract.

### Pegvisomant: metabolic and cardiac effects

Pegvisomant monotherapy does not have significant effects upon fasting insulin and glucose levels or the response to OGTT.[69] Treatment with pegvisomant also decreases left ventricular hypertrophy and improves systolic and diastolic function.[55] A transient increase in liver transaminases is observed in 25% of patients.[70] The mechanism is currently unknown, but a cross-sectional study recently found an association between the risk of hepatocellular injury and genetic polymorphisms associated with Gilbert's disease.[71] A more severe transaminitis (greater than three times the upper limit of normal) can be seen in 2.5% of patients and seems to be more prevalent in patients concurrently treated with somatostatin analogs.[60] Cotreatment with pegvisomant and somatostatin analogs was recently shown to increase intrahepatic lipid and decrease intramyocellular lipid compared to somatostatin analog therapy alone, which may serve as a possible explanation.[70]

### Dopamine agonists

Dopamine receptors are expressed by mixed prolactin/GH-secreting tumors as well as the majority of pure GH-secreting tumors.[72–74] Prior to the availability of somatostatin analogs, dopamine agonists were the sole medical therapy used to treat acromegaly for several decades. At that time, bromocriptine was relatively ineffective as a monotherapy, normalizing IGF-1 in only 10% of patients.[75] Cabergoline, a relatively newer dopamine agonist, tends to be better tolerated and more effective than bromocriptine. Higher response rates with normalization of IGF-1 in 20%–33% of patients have been reported in more recent studies using cabergoline.[76–78] In prior studies, pretreatment prolactin levels appeared to correlate with IGF-1 response rate to dopamine agonist therapy; however, this effect was not seen in the metaanalysis. Higher baseline prolactin levels did correlate with tumor shrinkage, which occurred in approximately one-third of patients. Patients with mild elevations in IGF-1 are most likely to benefit from dopamine agonists given that IGF-1 levels are lowered by 20%–30% with dopamine agonist monotherapy.[75] Cardiac valve abnormalities are a concern due to the data regarding cabergoline use in Parkinson's disease; however, a recent cross-sectional study found no difference in the prevalence of cardiac valvulopathy in patients treated with cabergoline (median dose 1 mg/week, range 0.5–3.5 mg/week) compared to acromegalic controls.[79] Cabergoline monotherapy may be safe, cost-effective, and medically appropriate in select patients with moderate elevations in IGF-1.

## Combination medical therapy

### Somatostatin analogs and pegvisomant

Combination therapy with somatostatin analogs and pegvisomant has been extensively studied in recent years. An early study by Feenstra et al demonstrated normalization of IGF-1 levels in 95% of patients previously uncontrolled by somatostatin analogs alone (either monthly octreotide LAR 30 mg or lanreotide ATG 120 mg) with the addition of weekly pegvisomant at a median dose of 60 mg/week.[80] In patients with active acromegaly despite octreotide LAR 30 mg every 28 days, adding pegvisomant 10–30 mg daily to the somatostatin analog was equally as efficacious as switching to pegvisomant monotherapy.[81] Theoretically, the action of somatostatin analogs to lower levels of circulating GH may lead to less competition of pegvisomant for the GH receptors, facilitating the use of lower and/or less frequent doses. The latter could result in cost savings and improved patient compliance and has been supported by recent studies suggesting that combination therapy can produce a sparing effect on the required doses of both agents.[82,83] An additional benefit of combination therapy relative to pegvisomant alone is the action of somatostatin analogs to induce significant tumor shrinkage in 20% of patients.[84]

A recent study showed that the use of somatostatin analogs and pegvisomant combination therapy is effective for up to 4.5 years, with normalization of IGF-1 levels in

95% of patients.[85] However, clinically significant elevations in transaminases are more frequent than with pegvisomant monotherapy and occur two times more frequently in patients with diabetes mellitus. As expected, the combination of pegvisomant and somatostatin analogs appears to worsen glucose control relative to pegvisomant monotherapy.[86] Presently, combination therapy with pegvisomant and somatostatin analogs presents significant safety concerns and is not US Food and Drug Administration approved, although several clinical trials are underway.

### Somatostatin analogs and dopamine agonists

Addition of a dopamine agonist to patients uncontrolled with somatostatin analogs alone can have significant benefits, particularly in patients with mild residual elevations in IGF-1. Studies have reported a 35% reduction in GH and IGF-1 levels with combination dopamine agonist and somatostatin analog therapy, resulting in normalization of IGF-1 in 37% of patients, particularly in a subgroup with elevated baseline prolactin levels.[87,88] A recent metaanalysis of 15 studies of 227 patients concluded that the addition of dopamine agonists reduced IGF-1 by 22%, leading to normalized IGF-1 in 50% of previously uncontrolled patients. In this analysis, the baseline prolactin level did not correlate closely with the biochemical response, although the degree of tumor shrinkage correlated with a higher serum prolactin level.[78] This treatment combination may be more favorable from a financial standpoint, given the relatively low cost of cabergoline. There are no reported safety concerns with the combination of somatostatin analogs and cabergoline as have been observed with somatostatin analogs and pegvisomant.

### Pegvisomant and cabergoline

In recent months, two studies have reported experience with the addition of cabergoline to pegvisomant monotherapy. In a retrospective study of 14 patients with a history of resistance to maximal doses of somatostatin analogs followed by suboptimal control with pegvisomant monotherapy (10–30 mg/day), the addition of cabergoline to pegvisomant monotherapy reduced IGF-1 levels by 18%, resulting in normalization of IGF-1 in 28% of patients, particularly if higher prolactin levels were present.[89] A recent prospective study followed 24 patients, many of whom had been treated with somatostatin analogs but some of whom were treatment naïve. On initial cabergoline monotherapy, only 11% of patients normalized IGF-1 levels. The addition of low-dose pegvisomant (10 mg/day) led to normalization of IGF-1 in 68% of patients, but only 26% of patients maintained normal IGF-1 levels on low-dose pegvisomant monotherapy 12 weeks after cabergoline was withdrawn. Only one patient had hyperprolactinemia, and there were no liver transaminase or glucose metabolism abnormalities.[90] Thus, dopamine agonist and pegvisomant combination therapy could have several benefits over pegvisomant combined with somatostatin analogs due to the ease of administration, improved side effect profile, and comparatively low cost of cabergoline. Further large prospective studies are needed.

## Novel medical therapies

### Pasireotide

Pasireotide (SOM230) is a novel somatostatin analog with affinity for SSTR1–3 and SSTR5. Relative to octreotide, the in vitro binding affinity of pasireotide is 40 times higher for SSTR5, 30 times higher for SSTR1, five times higher for SSTR3, and two times lower for SSTR2.[91] In phase II clinical trials where pasireotide was dosed twice daily subcutaneously, a biochemical response (defined as GH $< 2.5$ μg/L and normal age- and sex-matched IGF-1) was seen in 34% of patients after 3 months of therapy.[92] Additionally, 39% of patients had significant reduction in tumor volume $> 20\%$. Approximately two-thirds of patients had previously been treated with somatostatin analogs, and 23% of patients had no prior medical, surgical, or radiation therapy. All patients were treated with short-acting octreotide 100 μg subcutaneously three times daily for 1 month prior to beginning pasireotide therapy. Worsening of glucose metabolism was seen in 10% of patients, 5% of whom had an increase in hemoglobin $A_{1c}$ by 0.45% and 5% of whom developed overt diabetes mellitus.[93,94] Phase I clinical trials of pasireotide LAR demonstrated safety and efficacy,[95] and phase III clinical trials comparing pasireotide LAR to octreotide LAR and/or lanreotide ATG are currently underway (http://www.clinicaltrial.gov).

### Alternative delivery routes for octreotide

As well as developing novel somatostatin analogs that target different SSTRs, efforts to produce altered somatostatin analog formulations with improved or prolonged duration of action are being pursued. Octreotide implants lasting 6 months were previously in development, but despite acceptable safety and efficacy profiles in phase II and III clinical trials, development was halted in late 2011 (http://www.clinicaltrial.gov). An oral formulation of octreotide (Octreolin®; Chiasma Ltd, Jerusalem, Israel) performed similarly to subcutaneous octreotide with regard to pharmacokinetics and efficacy in phase I clinical trials.[96] It

**Table 1** Summary of medical therapies[92,95,96]

| Mechanism of action | Medication | Delivery | Dosing and frequency |
|---|---|---|---|
| **Currently available therapies** | | | |
| Somatostatin analog (first-generation) | Octreotide | SC | 100–200 mcg tid |
| | Octreotide LAR | IM | 20–40 mg every 4 weeks |
| | Lanreotide SR | IM | 30–60 mg every 7–14 days |
| | Lanreotide ATG | Deep SC | 60–120 mg every 4–8 weeks |
| GH receptor antagonist | Pegvisomant | SC | 10–30 mg daily |
| Dopamine agonist | Bromocriptine | Oral | 2.5–30 mg daily |
| | Cabergoline | Oral | 0.5–7 mg/week (divided twice weekly) |
| **Investigational therapies** | | | |
| Somatostatin analog (second-generation) | Pasireotide | SC | 200–600 mcg bid |
| | Pasireotide LAR | IM | 40 mg every 4 weeks† |
| | Octreolin® | PO | 40–80 mg daily† |

**Abbreviations:** ATG, autogel; GH, growth hormone; IM, intramuscular; LAR, long-acting release; PO, per oral; SC, subcutaneous; SR, sustained release; tid, three times daily.

utilizes the novel Transient Permeability Enhancer™ system (Chiasma) which facilitates paracellular transit of peptides across the gastrointestinal wall. Absorption of the drug was somewhat impaired by food as well as the use of proton pump inhibitors. The development of an oral treatment for chronic acromegaly is particularly relevant for patient quality of life, as injections of currently available somatostatin analogs can be associated with discomfort and local reactions. Recruitment for a phase III clinical trial is underway (http://www.clinicaltrial.gov).

## Preclinical studies

### Somatoprim

Somatoprim (DG 3173) is a heptapeptide with affinity for SSTR2, SSTR4, and SSTR5. It is the only reported agent with activity against SSTR4. The in vitro potency of GH suppression is 10,000 times greater than the suppression of insulin secretion. Somatoprim suppressed GH secretion in vitro in a higher percentage of adenomas than octreotide (ten of 21 versus five of 21). In addition, it was effective against six of 16 tumors that exhibited no response to octreotide and was more effective in sparsely granulated GH-secreting tumors.[97] The favorable effects upon insulin secretion may offer a theoretical benefit over pasireotide, although no direct comparative studies have been made. No clinical trials are yet underway.

### Dopastatin

Somatostatin receptors and D2 dopamine receptors have been shown to form heterodimers with increased functional activity.[98] Dopastatin (BIM-23A760), a D2 dopamine receptor/SSTR2 chimeric molecule that targets both receptors, showed promising in vitro activity against somatotroph tumors that had exhibited only partial response to somatostatin analogs.[99] Although this agent entered phase II clinical trials, these were terminated due to lack of efficacy in late 2010.

## Conclusion

Complete biochemical and clinical remission in acromegaly is often difficult to achieve with surgical resection alone. It is clearly established that significant morbidity and mortality can result from chronic, uncontrolled disease, and that suppression of GH and IGF-1 levels can minimize these detrimental effects. Over the past several years, significant progress has been made in the medical management of acromegaly and several effective monotherapies and combination therapies are now clinically available (Table 1). New agents that target additional GH-tumor receptors or creative combinations of existing agents that may improve compliance and decrease healthcare costs are actively under study, and several new therapies may soon be available.

## Disclosure

The authors report no conflicts of interest in this work.

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