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Management Options for Persistent Postoperative Acromegaly

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INTRODUCTION

Nearly one-third of patients with acromegaly will not be cured by initial surgery.[1] This statistic is likely attributable to the fact that growth hormone (GH)-secreting tumors are often large by the time they are discovered, because of the delayed recognition of acromegalic features.[2,3] Recently, the criteria for remission of acromegaly have become more stringent, meaning that an even larger number of individuals may be deemed not cured following surgery. To prevent the morbidity and early mortality associated with uncontrolled acromegaly, treatment options that provide prompt biochemical control while minimizing side effects are essential after unsuccessful surgery.[4] Choosing the appropriate therapy is best done in a multidisciplinary fashion involving close communication between endocrinologists, neurosurgeons, neuro-ophthalmologists, and radiation therapists. This review presents treatment approaches to the patient with persistent or recurrent postoperative acromegaly.

DEFINITIONS

Persistent disease denotes unsuccessful initial treatment, whereas recurrent disease is a return to a state of GH excess following initial remission. Despite advancements in surgical techniques, the cure rate following first-time surgery for acromegaly has not improved significantly over the last 30 years. A recent meta-analysis of 32 surgical series found persistent disease in 39% of patients while the recurrence rate following initial cure was only approximately 3%.[5] Thus, recurrence is much less likely than disease persistence to be encountered. From a management standpoint, the approach to persistent or recurrent disease is generally similar.

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Factors Predictive of Tumor Aggressiveness

Tumor size, extrasellar extension, and GH levels are the most important predictors of initial surgical cure.[6] Surprisingly, tumor size and invasiveness do not appear to predict the likelihood of tumor recurrence after remission.[5] Lower recurrence rate is observed in patients with low postoperative and glucose-suppressed GH levels, while age and gender have no predictive value.[5] The incidence of recurrences appears to peak around 1 to 5 years after surgery, although recurrences have been observed more than 10 years after initial cure.[5] Even with today's multimodal therapy, which can provide adequate disease control for the majority of patients, there is a subset of individuals (fewer than 10% of those cured surgically) who exhibit treatment-resistant tumor growth.[7] These factors have been associated with more aggressive tumor behavior[7]:

- Younger age at diagnosis
- Larger or extensive and invasive tumors
- Higher pretreatment GH levels
- Molecular and genetic factors
  - *gsp*, PTTG, GADD45 gene mutations
  - FGF-4 expression
  - MEN-1, AIP gene mutations[8]
- Tumor morphology
  - Sparsely granulated adenomas
  - Dotlike cytokeratin adenoma staining pattern
  - Higher Ki-67 index

Changing Biochemical Definition of Cure

A precise definition of cure has historically been challenging to reach in the absence of clear clinical parameters with which to monitor disease activity. Biochemical markers (insulin-like growth factor I [IGF-I] and GH) have therefore been relied on as the best indicators of disease burden. Higher GH and IGF-I are associated with increased mortality in acromegaly, often because of cardiovascular disease.[9] Thus, goals of therapy include normalization of IGF-I according to age-specific and sex-specific reference ranges, and attainment of GH levels below specific random and oral glucose-suppressed cutoffs. Over the last 50 years, the GH cutoff has been progressively lowered as GH assays have become more sensitive and specific. In fact, the postoperative basal GH criterion for cure in the 1960s was 10 to 20 times less stringent compared with today.[10] Up until the mid-1990s, GH was measured using polyclonal radioimmunoassay (RIA), and a GH treatment target of less than 2.5 μg/L was chosen as the criterion for cure based on data showing no incremental mortality risk below that level.[9] In 1999, taking into consideration the improved sensitivity of newer monoclonal GH assays (chemiluminescence, immunofluorescence, immunoradiometric, and so forth), a consensus group met in Cortina, Italy to propose criteria for cure. According to these Cortina criteria, a normal IGF-I level and nadir GH level after oral glucose tolerance test

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(GH_n) of less than 1 μg/L suggested cure.[11] That conference did not specifically mention a cutoff for random GH (GH_r), and several studies have used a cutoff of 2.5 μg/L as a definition of control.

Current Consensus Criteria for Cure

In the years following the publication of the Cortina criteria, significant advancements have been made in the management of acromegaly, particularly with respect to adjunctive medical therapy for persistent disease. The complex, often multimodal treatment in acromegaly, and the development of even more sensitive (ultrasensitive) GH assays led to newer criteria for cure (Table 1), published in 2010.[12]

Having only recently been implemented in practice, there are limited long-term outcome data to support the newer targets. The main evidence to date comes from 2 studies showing that mortality risk was similar to that in the reference population in patients whose GH_r was less than 1 μg/L.[13,14] There is a general consensus that using current ultrasensitive GH assays, a GH_r less than 1 μg/L corresponds to the older RIA GH value of 2.5 μg/L, for which a clear mortality benefit has been demonstrated.

Discordant IGF-I and GH

Generally, GH and IGF-I results are concordant following surgery; however, an elevated IGF-I despite normal GH may be seen in up to 24% of surgically treated patients, while high GH despite normal IGF-I is seen in about 10% of patients.[15,16] When there is discordance between IGF-I and GH results, determining the patient's clinical status can be perplexing, and often repeated testing is needed.

The reasons for discordant hormonal results after treatment are not entirely certain, although several possible causes have been identified (Fig. 1). The more common scenario of an elevated IGF-I with normal GH may result from inadequate GH sampling to detect elevated GH pulses, testing IGF-I levels too soon after surgery, low but uninterrupted GH secretion, and rare GH-receptor polymorphisms. The less common finding of a normal IGF-I with a high GH can result from any systemic condition that reduces hepatic IGF-I production. It is well known that medical treatment with somatostatin analogues (SSAs) is more likely to be associated with normal IGF-I despite elevated GH. This phenomenon has been attributed to pituitary-independent suppression of hepatic IGF-I production by SSAs.[17] A problem common to both scenarios is the issue of GH and IGF-I interassay variability, which has been discussed extensively in the recent American Association of Clinical Endocrinologists guidelines and current consensus criteria.[18,19]

Timing of Postoperative Biochemical Testing

Given the long biological half-life of IGF-I, accurate assessment of IGF-I status after surgery requires waiting at least 12 weeks for levels to stabilize.[20] On the other hand, GH has a very short half-life, and elevated values are telling even in the immediate postoperative period. The role of early (1 week postoperative) GH_n as a predictor of long-term remission has been examined in 2 studies.[20,21] Using GH_n cutoffs of 1.0 μg/L, these studies showed a high predictive value for cure based on early postoperative measurements. Although these

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cutoffs were higher than today's current standard, both studies showed high correlation between early postoperative (1 week) and delayed GH_n testing (12 weeks). This result suggests that an early GH_n by today's standard (<0.4 μg/L) probably predicts long-term remission. However, an early negative response to an oral glucose tolerance test requires follow-up testing at a later time point, because the inadequate sensitivity of this test may initially misclassify a patient in remission as having persistent disease.[20,21]

CLINICAL EVALUATION

In addition to targeting the source of the problem (excess GH), patients should be offered standard of care monitoring (ie, fasting lipid profile, blood pressure control, hemoglobin A_{1C}, and so forth), and treatments for their comorbidities (ie, blood sugar or lipid-lowering agents, osteoarthritis medications, bone-specific therapy, continuous positive airway pressure, and so forth). Worsening of a previously controlled symptom should prompt biochemical investigation for disease recurrence, and persistent symptoms might indicate the need for titration of medical therapy. Hypopituitarism is independently associated with reduced life expectancy, so anterior pituitary deficiencies resulting from the tumor or its treatment should be evaluated and appropriate hormone replacement started for any uncovered deficiencies.[22]

Radiological Evaluation

All patients who are not cured by surgery require follow-up pituitary magnetic resonance imaging (MRI) to determine residual tumor anatomy. It is generally advisable to wait at least 3 months before assessing radiographic response, to avoid misinterpreting postoperative inflammation and edema as tumor remnant. The need for MRI in cured patients is less obvious. When residual tumor is identified, its size, location, invasiveness, and mass effect (optic chiasm compression) are key considerations in determining the next management step. If optic chiasm compression is still present, formal visual field testing is important in establishing a new baseline before other treatment attempts. Repeat surgery is reasonable if the tumor is accessible, regardless of size. Cavernous sinus invasion is associated with a very low likelihood of successful repeat surgery.[23]

TREATMENT OPTIONS

After failed pituitary surgery, treatment options include:

- Repeat surgery
- Medical therapy
  - SSA
  - Dopamine agonist (DA)
  - Growth hormone receptor antagonist (GHRA)
  - Combination medical therapy (SSA ± DA ± GHRA)
- Radiotherapy

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- Conventional radiotherapy
- Stereotactic radiosurgery

A general treatment algorithm for persistent disease in proposed in Fig. 2.

Repeat Surgery

While surgery is generally the best initial treatment choice for acromegaly, medical therapy affords the best chances of remission after failed surgery and is the favored approach for persistent disease. In practice, repeat surgery is usually reserved for debulking purposes to increase the likelihood of remission with adjuvant therapies or when relief of mass effect on the optic chiasm is needed.

Effectiveness of Secondary (Repeat) Surgery

There is scant evidence on the effectiveness of repeat surgery. Among the handful of surgical series that have published outcomes of reoperations, only 5 used Cortina remission criteria (Table 2). The mean remission rate for reoperations in these contemporary series is 37%, but there is wide variation among the individual studies (8%–59%). When data from all the studies is combined, 117 of 345 reoperated patients achieved remission (34%), with the same remission rate seen when including only studies that used the Cortina criteria. As a reference, the mean remission rates from primary surgery using Cortina criteria in microadenomas, macroadenomas, and adenomas overall are 80%, 57%, and 64%, respectively.[1,24–26]

One of the major limitations in appraising the value of repeat surgery is the lack of clear inclusion criteria in the studies. When the investigators excluded tumors deemed unresectable on the basis of MRI appearance, the mean remission rate increased in individual studies by 12% to 36%, with an overall increase of 13% among pooled studies using the Cortina criteria.[27–29] For example, in a recent study by Alahmadi and colleagues,[29] when only noninvasive tumors were included in the calculations, 80% of persistent tumors (4 of 5 patients) were successfully cured. By contrast, in a much larger series of 140 reoperated patients by Nomikos and colleagues,[27] the remission rate only increased from 27% to 39% when invasive tumors with very high GH levels before first surgery were excluded.

In pooled data of all resectable tumors using the Cortina criteria, a remission rate of 47% is seen (55 out of 118 reoperations). While this efficacy rate is not significantly inferior to medical therapy (50%–60%), one must be cautious about directly comparing repeat surgery with medical therapy, given the much lower number of reoperated compared with medically treated patients described in the literature, the lack of consistently defined inclusion criteria, and varying durations of follow-up among these studies. Selection bias may actually overestimate the true remission rate if surgeons only choose to reoperate on those cases they believe have a high likelihood of being cured.

As is the case with primary surgery, the following were found to be predictors of unsuccessful repeat surgery:

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- Extradural or large suprasellar component[30]
- Cavernous sinus invasion[27,31,32] or carotid artery encasement[28]
- Tumor segmentation[23]
- GH level greater than 40 μg/L before first surgery[23]
- Younger age (<40 years)[23]

Among the combined patients in these series, 79% were persistent tumors while 21% were recurrences. It can therefore be assumed that most invasive tumors at repeat surgery had invasive features before the initial surgery. With the increasing specialization of pituitary surgery, failed initial surgery can more often than not be attributed to larger tumor size and invasiveness rather than lack of surgical expertise; however, if a patient has a residual tumor that appears completely resectable and lacks the aforementioned negative prognostic features (especially if the first surgery was performed by an inexperienced neurosurgeon), it is reasonable to consider repeat surgery by a more experienced pituitary surgeon. The surgeon's experience certainly should weigh heavily in the decision to consider repeat surgery, because several studies have demonstrated higher remission and lower complication rates when surgery is performed by a single experienced surgeon.[18,33,34]

Role of Debulking Surgery

Despite a low prospect of cure, repeated surgery can be used for the purposes of tumor debulking to increase the effectiveness of adjuvant medical therapy.[35,36] In a study of 86 patients poorly responsive to medical treatment with SSAs, partial primary surgical removal improved success rate from 12.8% to 55.5%.[36] Another study of 24 patients taking SSAs found that primary surgery increased the proportion of patients having normal GH and IGF-I from 29% to 54% and 46% to 78%, respectively.[35] Regarding the debulking benefit of secondary surgery, in a recent study of 53 patients whose preoperative GH was greater than 10 μg/L, partial tumor resection resulted in GH reduction below 10, 5, and 2.5 μg/L in 50%, 35%, and 21% of patients, respectively.[37] With respect to IGF-I, 17% of patients had a 30% reduction from preoperative levels while 9% achieved normalization.[37]

Risks of Repeat Surgery

Studies have reported varying incidences of new anterior pituitary hormone deficiencies after repeat transsphenoidal surgery. Yamada and colleagues[23] showed that among 31 reoperated patients almost all hormone deficiencies were acquired after thefirst surgery, with an incidence of new hormone deficiencies of only 1.9% after the second surgery. Recovery of pituitary function was seen in over one-third of patients after second surgery in another study.[32] By contrast, in their study of 53 reoperated patients, Espinosa de los Monteros and colleagues[37] showed nearly the same incidence of individual anterior pituitary hormone deficiencies after primary and secondary surgery. Because the mortality from untreated acromegaly exceeds that of hypopituitarism, and because hormone deficiencies can easily be replaced, the fear of worsening pituitary function should not bear heavily on the decision to consider repeat surgery.[22]

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Regarding operative morbidity, in the large study by Nomikos and colleagues[27] of 140 reoperated patients, the complication rates were comparable between primary and secondary surgery. However, the major complication rates from other surgical series (Table 3) were higher than expected based on data from first-time surgeries, likely because of the smaller sample size in these studies.[38] For example, meningitis, cerebrospinal fluid (CSF) leak, vascular injury, and ophthalmopathy are reported to occur in 0.7%, 2.2%, 0.6%, and 0.5% of major endoscopic series, respectively.[38] By comparison, in reoperated cases the incidence of meningitis was 1.8% to 6%, CSF leak/fistula 2% to 9%, vascular injury 0.1% to 6%, and ophthalmopathy 6%. There was no reoperative mortality in these series.

Medical Therapy

The 3 main classes of medications used in the treatment of acromegaly each have different receptor target actions:

1. The SSAs work by inhibiting somatotroph cell proliferation and GH secretion by binding to specific somatostatin receptors on GH tumor cells.
2. The DAs work by binding to the dopamine D2 receptor found on both GH and prolactin cells, thereby exerting negative control.
3. The GHRA, pegvisomant, blocks the peripheral target actions of GH.

Which class of medication to use for an individual patient depends on various factors, including the degree of active disease, tumor characteristics on MRI, underlying comorbidities, and cost. In general, SSAs are considered first-line medical therapy, as they have a long track record of efficacy as adjuvant therapy following surgery and/or radiotherapy. Because they offer both biochemical and tumor control, they should be used in patients with larger residual tumors. DAs, specifically cabergoline, might be considered in a patient with modest disease or if there is persistent hyperprolactinemia. Pegvisomant is usually reserved as third-line therapy because of its high cost and theoretical concerns about tumor growth, but might be considered in a patient with small tumor burden or persistent symptoms despite normalization of IGF-I.

SOMATOSTATIN ANALOGUES

The presently commercially available SSAs in the United States include octreotide, octreotide long-acting release (LAR) (Sandostatin LAR; Novartis, Basel Switzerland), and lanreotide autogel (ATG) (Somatuline Depot; Ipsen, Basking Ridge, NJ). Octreotide has a relatively short half-life of 2 hours after subcutaneous injection, meaning it has to be dosed 3 times daily to achieve therapeutic concentrations. Because of this inconvenient dosing schedule, it has been substituted in practice by the long-acting release form octreotide LAR, which can be administered by intramuscular injection once monthly. Lanreotide SR (sustained release) is an intermediate-acting formulation given every 1 to 2 weeks that is no longer available in the United States. It has been replaced by the longer-acting depot formulation, Lanreotide ATG, administered by deep subcutaneous injection once per month.

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Effectiveness as Secondary Therapy

Biochemical control—SSAs have been used as adjunctive therapy following surgery and/or radiotherapy for more than 20 years. The long-acting depot formulations, octreotide LAR and lanreotide ATG, are the 2 widely used medications in practice today. These drugs are conveniently dosed once monthly and show similar efficacy profiles. In recent years, SSAs have increasingly been used as primary therapy or as presurgical treatment to improve chances of surgical cure in macroadenomas. Given their broader uses in clinical practice, it is becoming harder to find studies using modern remission criteria that examine the efficacy of SSAs exclusively in surgically uncured patients. One such study of 68 patients showed that secondary SSA treatment achieved a biochemical remission (using Cortina criteria) in 64% and 78% of patients taking octreotide LAR and lanreotide ATG, respectively (no statistical difference between groups).[39] A selection bias (unresponsive patients excluded in this retrospective study) has likely contributed to the high percentage of remission. It has been shown that octreotide LAR has similar efficacy in both untreated patients and those who previously received surgery and/or radiotherapy, and that octreotide LAR and lanreotide SR are equally effective as secondary treatment.[40,41] Therefore, it is reasonable to assume that the efficacy of long-acting SSAs as secondary therapy approximates the overall efficacy among heterogeneous populations of untreated and previously treated patients. Among 32 studies, the long-acting SSAs are 63%, 56%, and 49% effective at normalizing GH, IGF-I, and both GH and IGF-I, respectively (Table 4).

Tumor shrinkage—In addition to biochemical control, prevention of tumor growth is an important goal of treatment with SSAs, particularly in the case of larger residual tumors. Octreotide LAR and lanreotide ATG exert pharmacologic effects on tumor growth by targeting distinct somatostatin receptors on GH adenomas. It has been suggested that the different receptor affinity profiles of these 2 medications may account for their subtle differences in effect on tumor shrinkage.[42] Most of the data on tumor shrinkage in acromegaly come from studies using either short-acting or long-acting formulations of octreotide and lanreotide SR, with sparse data regarding the effect of lanreotide ATG.[42]

Two factors may influence the effect of SSAs on tumor shrinkage: (1) whether the SSA is being used as primary or secondary therapy, and (2) tumor size. Although definitions of tumor shrinkage vary across studies, it has generally been shown that the SSAs can achieve greater tumor shrinkage when used as primary therapy. In treatment-naïve patients, 51% of patients treated with SSA had tumor shrinkage as compared with 27% after surgery or radiation.[43] Following noncurative surgery, the mean percentage of tumor-volume reduction has been shown to be similar between octreotide LAR (28.5%) and lanreotide ATG (34.9%).[39] With respect to tumor size, some studies have reported better response to shrinkage in macroadenomas compared with microadenomas, although this has not consistently been demonstrated.[42]

Whereas tumor shrinkage and biochemical parameters usually show parallel responses to treatment with SSAs, a dissociation between tumor shrinkage and biochemical response is occasionally observed (tumor shrinkage without biochemical control). If a patient who derives benefit from SSAs from the perspective of tumor control fails to achieve biochemical

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remission, consideration may be given to adding pegvisomant. The theoretical concern about tumor regrowth with pegvisomant would be lessened in the setting of concomitant use of an SSA that has been demonstrated to exert tumoral control.

Symptom control—The SSAs can provide effective symptomatic control after noncurative surgery. In a study of 33 patients with poorly controlled disease requiring multimodal therapy (surgery, radiation therapy, DAs), octreotide LAR resulted in 54% reduction in the prevalence of clinical signs and symptoms at follow-up of nearly 3.5 years.[44] In this cohort of patients, of whom 39% had invasive adenomas, the reductions in acromegalic symptoms were 28%, 38%, 40%, and 70% for arthralgias, perspiration, asthenia, and acral growth, respectively.[44] In a study of 131 patients taking lanreotide ATG, of whom 76% had had prior surgery, there were improvements of 11%, 16%, 14%, 24%, and 16% in sweating, headache, asthenia, edema, and arthralgias, respectively.[45]

Predictors of response—Responsiveness to SSAs is inversely correlated with tumor size and baseline hormonal levels. Smaller, less invasive adenomas with lower GH and IGF-I are more likely to reach biochemical control. Although prior surgery or radiotherapy does not influence the GH response to SSAs, radiotherapy has been associated with a less marked lowering of IGF-I.[46] It has been suggested that the pathologic finding of a densely granulated adenoma and a hypointense T2-weighted MRI signal in acromegalic patients after failed surgery may both predict a better response to SSA treatment.[47,48]

Clinical Considerations

Dose optimization—The response to usual starting doses of SSAs may vary considerably among patients, with respect to both biochemical and symptom control. Doses should be optimized before considering a patient to be a nonresponder. As long as there are no limiting side effects, doses should be increased up to a maximum of 40 mg per month for octreotide LAR (requiring 2 separate injections) and 120 mg per month for lanreotide ATG (maximal doses approved by the Food and Drug Administration). Likewise, the minimal dose required to attain biochemical and symptomatic control should be used.

Recently it has been shown that high-dose or high-frequency treatment with SSAs can improve their efficacy in patients considered refractory to treatment with these drugs.[49] When patients unresponsive to conventional doses of octreotide LAR are switched to high doses (60 mg/mo) or high-frequency dosing (30 mg/3 wk), 27% and 36% achieved control of GH and IGF-I, respectively.[49] There is less experience with high-dose or high-frequency lanreotide ATG; however, a small case series showed 5 of 6 patients achieved GH normalization and 3 of 6 had normalization of IGF-I when lanreotide ATG was sequentially titrated to 180 mg every 3 to 4 weeks.[50]

Side effects—Even at maximal doses, the safety and tolerability of SSAs is generally maintained, with the most common side effects related to gastrointestinal symptoms: abdominal cramps, flatulence, diarrhea, constipation, and nausea.[49,51] Abnormalities of the biliary tract, including gallstones, sediment, sludge, and dilatation occur fairly commonly within the first 2 years of treatment regardless of dose, although they are usually

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asymptomatic and rarely require surgery. Patients should be questioned about cholelithiasis symptoms at follow-up, but abdominal ultrasound surveillance is not necessary.

Local skin irritation and pain at the injection site may be experienced, but is usually mild and dose dependent. One of the advantages of lanreotide ATG is that, unlike octreotide LAR, the formulation does not have to be reconstituted by a health care professional before administration, and can safely be administered at home by the patient or partner.[52]

With respect to glucose homeostasis, surgery may have a greater effect on reversal of impaired glucose tolerance and type 2 diabetes in comparison with primary therapy with SSAs. This outcome is believed to be due to the negative effects of SSAs on pancreatic β-cell function.[53] However, because GH itself is associated with insulin resistance, SSAs generally have a neutral effect on glycemic control.[54] Also, the addition of GHRA to SSA does not appear to significantly alter glycemic control.[55]

DOPAMINE AGONISTS

The DAs, cabergoline and bromocriptine, are traditionally used in the management of prolactin-secreting pituitary adenomas. Their use in acromegaly is based on the fact that both mixed prolactin-GH and pure GH-secreting adenomas have dopamine receptors on their surfaces.[56] Indeed, even patients without hyperprolactinemia may show a marked biochemical response to cabergoline.[56] The advantages of the DAs are that they are relatively inexpensive compared with other medical therapies and can be taken orally.

In the United States there are 2 commercially available DAs: cabergoline and bromocriptine. Cabergoline is the preferred drug in this class, both for the management of prolactinomas and GH-secreting adenomas, because of its longer half-life, superior efficacy, and better tolerability compared with bromocriptine. Therefore, this review focused mainly on the efficacy of cabergoline in persistent postoperative acromegaly.

Effectiveness as Secondary Therapy

Biochemical control—As monotherapy, cabergoline normalizes IGF-I in less than one-third of patients, and when combined with SSAs, its efficacy increases to about 50%.[56] Therefore, the authors reserve it for those patients who do not completely normalize serum IGF-I with SSA monotherapy (particularly if serum IGF-I levels are less than 2 times normal). As with other treatments in acromegaly, the most significant predictor of responsiveness to cabergoline is the baseline IGF-I level: chances of remission are greatest when IGF-I is less than 150% the upper limit of normal.[56] Prior surgery is not associated with any differences in response to DAs, while prior radiotherapy actually shows an enhanced response to GH reduction.[46] Unfortunately, most of the studies assessing the efficacy of cabergoline as adjuvant or primary therapy did not use the Cortina criteria but rather relied solely on normalization of IGF-I as the indicator of response.[56]

Tumor shrinkage—There is limited prospective data regarding the effect of DAs on tumor shrinkage. Studies differ with respect to the DA used, the proportion of previously operated patients, and definitions of tumor shrinkage.[56] A recent meta-analysis found that cabergoline

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was shown to reduce tumor volume to varying extents in 17 of 32 patients.[56] Although it cannot predict biochemical response, the presence of hyperprolactinemia may result in a greater degree of tumor shrinkage by cabergoline.[56] Therefore it might be considered in patients with modest disease who have elevated serum prolactin levels.

Dose escalation—The cabergoline dose required for biochemical control in acromegaly can be variable, but averages around 2.5 mg/wk, which is 2 to 5 times higher than doses used to treat prolactinomas.[56] Nonetheless, adverse effects do not appear to be increased as a result of this higher dose.[56] Recently, concerns have been raised about the possibility of cardiac valvular disease in individuals taking high cumulative doses of DAs, as in Parkinson disease. Although this effect has not been clearly demonstrated in patients being treated for prolactinomas, because acromegaly itself confers an increased risk of cardiomyopathy and valvulopathy it may be prudent to monitor patients on higher doses of cabergoline with periodic echocardiograms.[56]

Side effects—Cabergoline is generally well tolerated. The main side effects are nausea and vomiting, followed by headaches, nasal congestion, and dizziness.[56] Bromocriptine causes more pronounced gastrointestinal side effects, with nausea and vomiting occurring in up to one-third of patients.[57] These side effects can be minimized by starting with a low dose and titrating slowly.[57]

PEGVISOMANT

Pegvisomant is a genetically modified GH analogue that acts as a competitive inhibitor at the receptor level to block the action of native GH. Because of its mechanism of action, pegvisomant has no effect on tumor shrinkage. For this reason, and because of its very high cost, pegvisomant is almost never used as monotherapy to treat persistent postoperative disease.[10,58] However, it can play an important role in patients refractory to SSAs or DAs. The medication is administered by subcutaneous injection daily, although less frequent injections in combination with SSAs are also highly effective and offer a financial advantage in patients who might otherwise require high doses of pegvisomant.[59] Average therapeutic doses range from 15 to 20 mg/d, but doses up to 60 mg/d have been used. Because pegvisomant has no effect on GH secretion, serum IGF-I levels serve as a gauge of biochemical remission.

Efficacy as Secondary Therapy

Monotherapy—Initial studies using pegvisomant, which included large numbers of patients who had failed surgery or radiotherapy, found the drug to highly effective at normalizing IGF-I levels (90%–95% of patients) and controlling acromegalic symptoms.[60] Recently, however, this has been brought into question by the results of the large observational Acrostudy of 792 patients, which showed that fewer than 70% of patients had achieved normal IGF-I levels at 5-year follow-up.[61] One of the reasons for this disappointing result may be inadequate dose titration of pegvisomant in study participants, because a large proportion of the patients with high IGF-I were receiving a daily dose of 20 mg or less

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(which is the highest vial size presently available, but below the maximal dose used in clinical trials of 40 mg/ d).[61]

Combination pegvisomant and SSA—In practice, pegvisomant is often considered for the patient who is suboptimally controlled on SSA therapy. A recent study of 27 patients who had previously undergone surgery or radiotherapy and who failed to achieve remission with octreotide LAR found that pegvisomant, whether added onto octreotide LAR or used as monotherapy, was equally effective at normalizing IGF-I (56% as monotherapy, 62% in combination).[62] Similar findings have been observed with lanreotide ATG[63]; however, the lower than expected efficacy seen with the combination of lanreotide ATG and pegvisomant (58%) may be due to the purpose of the study, which focused on the cost-savings benefit of combination therapy. The investigators showed that the dose of pegvisomant could be reduced by the addition of lanreotide ATG, but the full potential of combination therapy may not have been realized because the emphasis was on pegvisomant dose reduction rather than maximization.[64] Indeed, it has been shown that weekly dose reductions of pegvisomant of 80 to 150 mg could be achieved by the addition of lanreotide ATG, with no change in serum IGF-I levels.[64] While this may translate to substantial cost reductions for the patient, it may also come at the expense of inadequate IGF-I control. Therefore, if pegvisomant is to be considered in treatment it should be titrated maximally to guarantee the most effective response.[60] Finally, because of pegvisomant's favorable effects on glucose control, some believe that it should be the first-choice medical therapy in patients with diabetes.[65]

Combination pegvisomant and cabergoline—To date, there is only a single study of 24 patients assessing combination pegvisomant and cabergoline therapy.[66] In this study, 96% of patients had a history of noncurative surgery. As monotherapy, cabergoline normalized IGF-I levels in only 8% of patients, but with the addition of low-dose pegvisomant (10 mg daily) 68% of patients achieved a normal IGF-I. Surprisingly, after being withdrawn from cabergoline treatment, only 26% of patients treated with pegvisomant monotherapy had normal IGF-I levels. This result suggests that the combination of cabergoline and pegvisomant is more effective than either agent alone.

Symptom control—It has been argued by some that normal IGF-I levels alone should not be the sole indicator of clinically controlled acromegaly.[67] A double-blind, placebo-controlled study showed that antagonizing GH action using pegvisomant in patients who had already normalized serum IGF-I levels on SSA improved quality of life.[67] This effect appeared to be mediated by improvement in GH-dependent parameters, such as loss of body weight, reductions in perspiration, and soft-tissue swelling.[67] The concept of extrahepatic acromegaly has been coined to explain this phenomenon: while SSAs, in addition to reducing GH secretion, inhibit the action of GH at the liver (where IGF-I is produced), they do not necessarily target the GH actions in other organs. As a result of the marked improvement in quality-of-life scores, some have questioned whether pegvisomant should only be reserved for patients who fail SSA treatment and should instead be used more liberally.[64]

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Risk of tumor growth—Because pegvisomant blocks the negative feedback inhibition of IGF-I on GH cells, there is a theoretical concern that the medication could exacerbate tumor growth. Although there have been case reports of tumor growth in patients taking pegvisomant, it is unclear whether this simply reflects selection bias (ie, more aggressive tumors end up requiring pegvisomant) or whether this may be a rebound effect after withdrawal of SSAs.[68] In the large Acrostudy, the incidence of tumor growth on pegvisomant was 5%, which was slightly higher than the expected 2.2% risk of tumor progression in patients taking SSAs.[69] Given the uncertainty regarding tumor growth, it is advisable not to use pegvisomant as first-line single therapy in patients with large macro-adenomas in close proximity to the optic chiasm, and all patients taking pegvisomant should be monitored with serial MRIs at 6-month intervals initially.[18]

Side effects—Pegvisomant is usually well tolerated. A commonly reported adverse effect is elevations in liver transaminases, which is usually asymptomatic and transient even with continuation of the drug. Despite this, regular monitoring of liver function tests is necessary in patients taking pegvisomant. Some patients develop local fat accumulation in the injection areas (lipohypertrophy), believed to be due to the local anti-GH effect on lipolysis. Other uncommon side effects include fatigue, dizziness, headaches, perspiration, and abdominal bloating.[61]

FINANCIAL CONSIDERATIONS WHEN CHOOSING MEDICAL THERAPY

An important factor to consider when choosing adjuvant medical therapy is what financial implications it will have for the patient and society. Although surgery has a high upfront cost, medical treatment is much pricier in the long term.[68] Among the medications, cabergoline is approximately one-fifth the price of a long-acting SSA.[68] If financial constraints pose a barrier to standard treatment, one might consider using the short-acting octreotide, which is appreciably less expensive than the long-acting formulation. Alternatively, in patients with modest disease, a trial of cabergoline monotherapy is a reasonable first option. Pegvisomant can cost $30,000 to $90,000 per year, which is one of the main barriers to its implementation in practice.[10]

EMERGING MEDICAL THERAPIES IN ACROMEGALY

An exciting novel somatostatin analogue is anticipated to join the armamentarium of acromegaly treatments. Unlike octreotide and lanreotide, pasireotide (SOM230) has high affinity for both of the somatostatin receptor subtypes (types 2 and 5) expressed by most GH-secreting adenomas.[70] The durable effect of pasireotide on IGF-I levels suggests a longer half-life compared with octreotide.[71] Preliminary studies have suggested superiority over octreotide; however, results of the phase III randomized trial concluded about 1 year ago are needed to compare the efficacy of this newer agent with that of the existing long-acting SSAs.

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RADIATION THERAPY

Radiation therapy (RT) is generally considered the last resort for patients with persistent postoperative acromegaly given the unfavorable side-effect profile and the delayed time to achieve biochemical effect. The indications for its use include uncontrolled GH secretion, tumor growth, or both. Whereas the control of tumor growth can be rapid following pituitary RT, biochemical remission can take years to decades to be achieved. Thus, patients often require continued medical therapy while awaiting the effects of radiation on GH secretion.

Conventional RT

Conventional RT consists of delivery of repeated doses of 160 to 180 cGy several days per week over a 5- to 6-week period for cumulative doses of 4500 to 5000 cGy.[68] The radiation is delivered mainly from 2 to 3 portals while the patient is immobilized wearing a tight-fitting mask, allowing an accuracy of 2 to 5 mm.[68]

Effectiveness—With the evolving biochemical definitions of remission and improved sensitivities of GH assays, the remission rates following RT have declined over the years. In studies that use the Cortina criteria, remission rates of 10% to 60% have been reported.[68] There is an average delay to remission following conventional RT of 10 years, with a predictably longer latency period in patients with high GH and IGF-I levels.[68] Therefore, the majority of patients are continued on medical therapy while awaiting the effect of RT. With respect to tumor control, conventional RT results in tumor shrinkage in 50% and maintains tumor control in up to 90% of patients at 10 years.[68]

Complications—Owing to the unintended radiation exposure to the normal pituitary gland, there is a high incidence of hypopituitarism following fractionated RT. More than half of patients will develop hypopituitarism at 5 to 10 years, with a progressive increase in the incidence over time. This risk appears to be dose dependent. Because hypopituitarism has independently been associated with reduced life expectancy, patients need regular endocrine testing and treatment of any identified hormonal deficiencies.

A rather alarming fact, however, is that even when corrected for hypopituitarism, fractionated RT may be associated with an increased mortality risk. In a study of 501 patients with acromegaly, all-cause mortality in patients who received fractionated RT was increased at 14-year follow-up, with a standardized mortality ratio of 1.58 (95% confidence interval 1.22–2.04).[22] Similar findings have been observed in 2 other large registries of acromegalic patients.[22] The main cause of death in all of these studies is cerebrovascular or cardiovascular disease.[22] Indeed, among patients who received RT for several pituitary conditions, an underlying diagnosis of acromegaly was one of several predictors of a cerebrovascular accident. It appears that prior surgery may also play a role in the mortality after fractionated RT. Although the possibility of selection bias (more aggressive tumors are more likely to require RT) needs to be clarified further, most pituitary centers are shifting away from conventional RT and using radiosurgery when necessary. That being said, the long-term outcome data for radiosurgery remain limited.

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In addition to damage to the pituitary gland, patients often fear vision loss caused by optic neuropathy following RT. However, with modern MRI techniques and surgical debulking before RT, this risk is very low.

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) encompasses several modalities, including Gamma Knife, Cyber Knife, and Primatom linear accelerator. Most of the experience to date in acromegaly using SRS involves Gamma Knife, which delivers γ-radiation though a hemisphere placed around the patient's head. The increased precision from this modality results from the fact that several beams of radiation must align to target a specific location.

Effectiveness—In a recent meta-analysis of 25 studies of SRS treatment in acromegaly, only 12 used Cortina remission criteria.[72] In these studies the remission rate was 45%, with a mean duration of reported follow-up of 4.6 ± 1.7 years.[72] When all of the studies were included in the analysis, an overall disease control rate of 48% was seen after SRS (without adjuvant medical therapy). The majority of the patients studied were refractory to medical therapy before SRS, but 14% to 17% achieved the defined remission criteria on the same doses of medication after SRS.[72] With respect to tumor control, data from 45 surgical series including 1350 patients showed that SRS is 97% effective at stabilizing or reducing tumor volume.[73] Because the effects of SRS may not be realized for years following treatment, determining the ultimate efficacy of SRS in acromegaly will require review of studies with longer follow-up intervals.

Complications—There is a lack of long-term follow-up data on SRS. As with conventional RT, the main side effect is hypopituitarism, with new-onset anterior pituitary deficiencies reported in as many as 47% of patients.[73] It is difficult to define the true incidence of SRS-induced hypopituitarism because many study patients had received prior conventional RT.[73] Other side effects of SRS include visual complications, cranial neuropathies, seizures, and carotid artery stenosis, although these were relatively uncommon.[73] The low rates of visual complications following SRS has been linked to the lower radiation exposure to the optic apparatus (8–10 Gy).[73]

AREAS OF UNCERTAINTY

At present, the biochemical assessment of disease activity in acromegaly is replete with uncertainty, primarily resulting from the following issues:

- Unacceptable variability in IGF-I and GH assays
- Lack of uniformity in methods of assessment
- Treatment goals based on historical data derived from older hormone assays

Further studies are needed to clarify:

- Clinical implications of GH_n in borderline range (0.1–0.4 μg/L) and normal IGF-I

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- Whether GH actions should be targeted even in the context of a normal IGF-I with the use of pegvisomant
- Long-term safety data following SRS
- Efficacy of all currently available treatment modalities using the stringent 2010 remission criteria

SUMMARY

Persistent or recurrent acromegaly after noncurative surgery can be challenging to treat. However, with the various treatment modalities available today, most patients are ultimately able to achieve biochemical remission and control of tumor growth by some means. The SSAs are usually the first-line therapy after noncurative surgery, but repeat surgery might be considered if the tumor is surgically accessible and an experienced pituitary surgeon is available. Surgical debulking may also improve the chances of remission with medical therapy. In cases of SSA resistance, options include the addition of cabergoline or pegvisomant. Radiotherapy, particularly SRS, should be reserved for those patients who are resistant to other treatments, given the uncertainties about long-term risks.

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KEY POINTS

- Control of growth hormone (GH) and insulin-like growth factor I (IGF-I) levels is often not complete after surgery.
- Second surgery may be considered if an anatomic target is evident or to further reduce GH levels.
- Somatostatin analogues (SSAs) are the first line of medical therapy.
- Pegvisomant can be added or switched to if SSAs do not reach control.
- Radiation therapy has good tumor growth control, but hormonal control may require many years.

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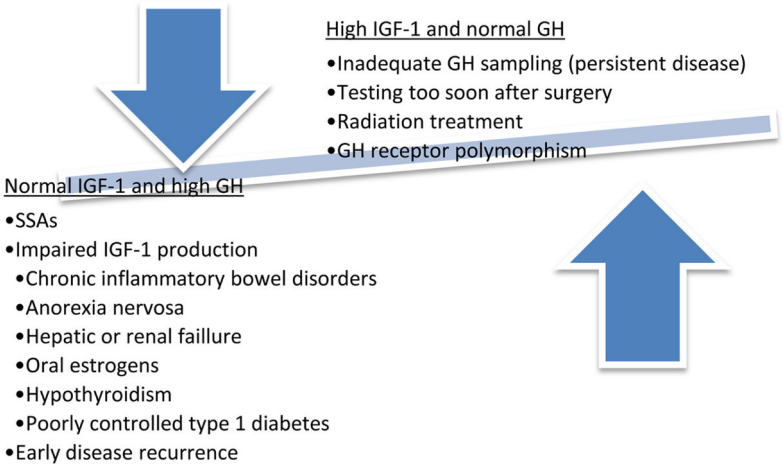

Fig. 1.

Possible causes of discordant IGF-I and GH results. SSA, somatostatin analogue.

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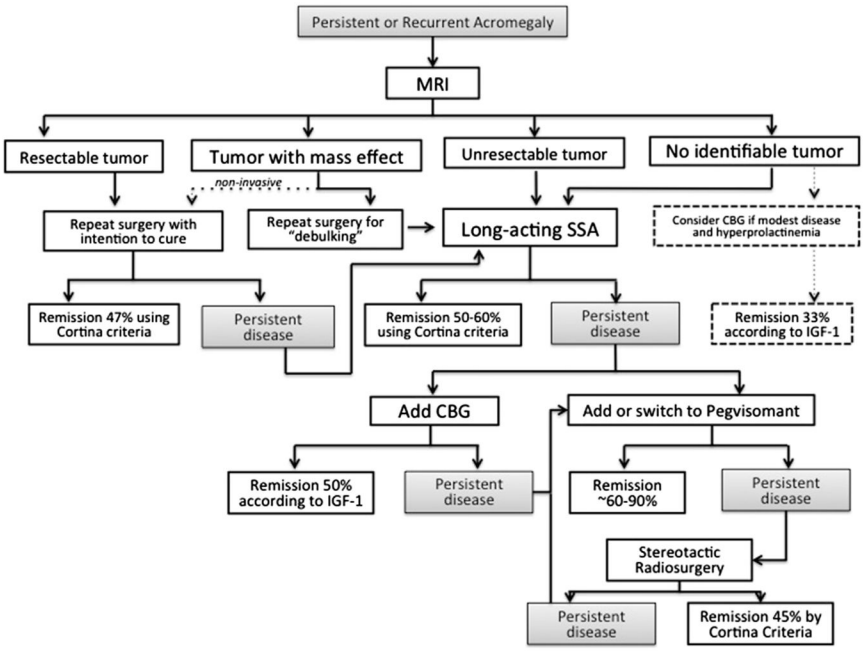

Fig. 2.

Treatment approach for persistent postoperative acromegaly. CBG, cabergoline; SSA, somatostatin analogue.

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Table 1

Biochemical criteria for cure in acromegaly

Consensus Criteria	Random Fasting GH (GH_r) (μg/L)	Nadir GH After OGTT (GH_n) (μg/L)	IGF-I
2000 Cortina criteria	(Not defined)	<1	Age/sex normalized
Current 2010 criteria	<1	<0.4	Age/sex normalized

Abbreviation: OGTT, oral glucose tolerance test.

(*Data from* Giustina A, Barkan A, Casanueva FF, et al. Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 2000;85:526–9; and Giustina A, Chanson P, Bronstein MD, et al. A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab 2010;95:3141–8.)

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Table 2

Outcomes of repeat surgery for persistent or recurrent acromegaly after surgical treatment

Authors,[Ref.] Year	Remission Criteria: Normal IGF-I and		Total No. of Patients	No. of Reoperated Patients	No. of Persistent/ Recurrent Patients (% of Each)	Remission Rate (%)	Remission Rate Among Resectable Tumors Only (%)
	GH_n (μg/L)	GH_r (μg/L)					
Long et al,[30] 1996	<2	<5	212	16	12/1[a] (75/6)	5/16 (31)	NR
Freda et al,[31] 1998	<2	<2	115	12	2/10 (17/83)	4/12 (33)	NR
Abe and Lüdecke,[32] 1998	<2	<4.5	270	28	26/2 (93/7)	16/28 (57)	16/18 (89)
Shimon et al,[74] 2001	<2	<2	103	12	12/0 (100/0)	1/12 (8)	NR
Kurosaki et al,[28] 2003	<1	<2.5	NR	22	18/4 (82/18)	13/22 (59)	13/16 (81)
Nomikos et al,[27] 2005	<1	<2.5	688	140	98/42 (70/30)	38/140 (27)	38/97 (39)
Espinosa de los Monteros,[37] 2009	<1	-	NR	53	53/0 (100/0)	5/53 (9)	NR
Yamada et al,[23] 2010	<1	NR	482	53	NR	31/53 (58)	NR
Alahmadi et al,[29] 2012	<1	<2.5	350	9	NR	4/9 (44)	4/5 (80)
All studies combined				345	221/59 (79/21)	117/345 (34)	71/136 (52)
Combined studies that used Cortina criteria				277	169/46 (79/21)	91/267 (34)	55/118 (47)

Abbreviations: GH_n, post-OGTT GH nadir; GH_r, random fasting GH; NR, not reported.

[a] Indication for surgery was visual impairment for 4 tumors, not specified as persistent or recurrent.

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Table 3

Complications following repeat surgery

Authors,[Ref.] Year	Operative Mortality Rate, %	Overall Complication Rate, %	Major Complications (Rate, %)
Long et al,[30] 1996	0	19	SAH, intrasellar hemorrhage (6) New bitemporal hemianopsia (resolved) (6) Bacterial meningitis (6) CN III, IV, VI palsies (6)
Abe and Lüdecke,[32] 1998	0	0	
Kurosaki et al,[28] 2002	0	0	
Nomikos et al,[27] 2005	NR	Similar to primary surgery	Overall complications(primary and secondary surgery): Meningitis (1.8) CSF leak (0.8) Carotid artery injury (0.1)
Espinosa de los Monteros et al,[37] 2009	0	21	Arachnoid tear (8) CSF fistula (9) Meningitis (2) CSF fistula + meningitis (2)
Yamada et al,[23] 2010	0	13	CSF leak (3) CN VI palsy (3) Severe nasal bleeding (3) Pituitary abscess (3)

Abbreviations: CN, cranial nerve; CSF, cerebrospinal fluid; NR, not reported; SAH, subarachnoid hemorrhage.

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Table 4

Biochemical remission rates achieved using long-acting SSAs as both primary and secondary therapy

Authors,[Ref.] Year	% of Patients Achieving GH Criteria for Remission	% of Patients with Normalized IGF-I	% of Patients Achieving Both GH Criteria for Remission and Normalized IGF-I
Octreotide LAR			
Lancranjan and Atkinson,[75] 1999	69.8[a]	63.1	NR
Chanson et al,[76] 2000	68[a]	NR	65
Colao et al,[77] 2001	69.4[a]	61.1	NR
Ayuk et al,[78] 2002	36[b]	67	NR
Ayuk et al,[40] 2004	70[b]	72	NR
Alexopoulou et al,[79] 2004	64[a]	52	NR
Jallad et al,[80] 2005	74[a]	41	NR
Grottoli et al,[81] 2005	64[a]	35.7	28.6
Trepp et al,[82] 2005	NR[a]	NR	65
Cozzi et al,[83] 2006	68.7[a]	70.1	56.7
Colao et al,[84] 2006	NR[a]	NR	55.9
Ronchi et al,[85] 2007	43[a]	35	NR
Maiza et al,[86] 2007	70[b]	67	58
Mercado et al,[87] 2007	42[a]	34	25
Colao et al,[88] 2007	86[a]	84	80
Auriemma et al,[89] 2008	77.7[a,b]	62.9	62.9
Colao et al,[90] 2009	NR[a]	NR	27.5
Baldys-Waligorska et al,[91] 2009	63[a,b]	54.5	NR
Oki et al,[92] 2009	56.7[a]	53.3	36.7
Luque-Ramirez et al,[93] 2010	54[a]	46	NR
Tutuncu et al,[39] 2011	67[c]	67	63.9
Karaca et al,[26] 2011	45[c]	27	27
Octreotide LAR (nonweighted mean ± SD)	63 ± 13	55 ± 15	50 ± 19
Lanreotide Autogel			
Caron et al,[94] 2002	NR[a]	NR	39
Alexopoulou et al,[79] 2004	48[a]	52	NR
Caron et al,[45] 2004	68[a]	NR	43
Caron et al,[95] 2006	77[a]	54	46
Lucas and Astorga,[96] 2006	54[a]	56	40

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Authors,[Ref.] Year	% of Patients Achieving GH Criteria for Remission	% of Patients with Normalized IGF-I	% of Patients Achieving Both GH Criteria for Remission and Normalized IGF-I
Ronchi et al,[85] 2007	62[a]	43	NR
Chanson et al,[97] 2008	85[a]	43	38
Melmed et al,[98] 2010	49[a]	54	38
Lombardi et al,[99] 2009	63[a]	37	NR
Attanasio et al,[100] 2008	42[a]	54	38
Salvatori et al,[52] 2010	76.9[c]	84.8	73.1
Tutuncu et al,[39] 2011	78.1[c]	78.1	78.1
Schopohl et al,[101] 2011	71.4[b]	62.9	NR
Lanreotide Autogel (nonweighted mean ± SD)	65 ± 14	56 ± 14	48 ± 16
Both long-acting SSAs (nonweighted mean ± SD)	63 ± 13	56 ± 15	49 ± 17

Abbreviation: NR, not reported.

[a] GH_T <2.5 μg/L.

[b] GH_T <2 μg/L.

[c] GH_n <1 μg/L.