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REVIEW

Newer options in the management of acromegaly

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Abstract

Paradigms for managing acromegaly have undergone major changes in the past two decades. This has been brought about by combining surgical, pharmacological and radiotherapeutic approaches that provide tight biochemical control to reduce mortality to that of the general population. The biochemical targets for treatment are a growth hormone of <2.5 ng/mL (~7.5 mU/L) and a normal, age-adjusted insulin-like growth factor-1. Until 20 years ago, dopamine agonists were the only class of pharmaceutical agents available to control acromegaly. They have a limited adjunctive role, even with the development of second-generation selective agonists such as cabergoline. Surgery and radiotherapy were the mainstay of acromegaly management before the advent of the effective pharmacological therapies of the modern era: somatostatin analogues and pegvisomant, a growth hormone receptor antagonist. Somatostatin analogues achieve biochemical control in approximately 60% of patients. Pegvisomant, which is available in the USA and Europe and has just been registered in Australia, normalizes insulin-like growth factor-1 in nearly all patients but has no effect on tumour mass. Surgery is an appropriate first-line therapy for microadenomas as the chance of success is high. For large and/or invasive tumours where the prospect of surgical cure is remote, first-line therapy is somatostatin analogue treatment with debulking surgery having an adjunctive role to achieve tight control or to alleviate compression of the optic chiasm. Although acromegaly remains a challenging disease to manage, the expanding range of therapeutic options is likely to result in a better outcome for patients and offers the potential to tailor therapy based on a patient's individual requirements.

Introduction

Acromegaly is caused by excessive growth hormone (GH) secretion, with the vast majority of cases caused by a pituitary GH-secreting adenoma. Traditional management of acromegaly consisted of surgery as initial therapy, followed by radiotherapy if disease control was not achieved. Advances in neuroendocrine physiology and pituitary cell biology have resulted in the development of new pharmacological approaches that are challenging surgery as the primary mode of therapy, as they allow effective biochemical control in nearly all patients for the first time ever. The importance of achieving true biochemical remission in acromegaly is underscored by unequivocal evidence that this normalizes mortality rate. Management of acromegaly is currently changing and likely to result in a better outcome for patients with this difficult disease.

This article will first define therapeutic goals in the modern management of acromegaly. Using these targets, the efficacy of the traditional approach of surgery and/or radiotherapy will be compared with newer pharmacological therapies for acromegaly, specifically somatostatin

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analogues, selective dopamine receptor agonists and the GH receptor antagonist, pegvisomant. Given the expanding therapeutic options for acromegaly, we will also recommend a framework for combining different therapies in the management of acromegaly.

Therapeutic aims in the management of acromegaly

Acromegaly increases mortality and causes substantial morbidity. Overall survival in patients with acromegaly treated with surgery and/or radiotherapy is reduced by 10 years, and this reduction strongly correlates to the level of residual biochemical disease activity.[1] Mortality rates for acromegaly are 1.6–3.0 times greater than that of the general population, predominantly from cardiovascular and respiratory disease.[2,3] The findings of several excellent epidemiological studies from New Zealand and overseas have enforced a revision of the biochemical targets of treatment. These studies report that therapy which reduces GH to <2.5 ng/mL (~7.5 mU/L) or insulin-like growth factor-1 (IGF-1) into the age-adjusted reference range reduces mortality rates to that of the general population.[1,4–7]

Treatment of the comorbidities associated with acromegaly is equally important as these have an effect directly or indirectly on mortality. Hypertension, impaired glucose tolerance and obstructive sleep apnoea are prevalent in acromegaly and are established risk factors for cardiovascular disease. Most studies have not examined the contribution of comorbidities to excess mortality in acromegaly. However, Holdaway *et al.* found both diabetes and hypertension to be more prevalent in deceased patients than in surviving patients with acromegaly, with the presence of hypertension at last follow up an independent predictor of mortality.[6] Sleep apnoea is found in up to 80% of patients with acromegaly and is a likely codeterminant of cardiovascular mortality if untreated.[8]

The goal for treatment of acromegaly is to restore GH hypersecretion to normal and to achieve complete tumour removal without compromising pituitary function. However, this goal is elusive in most patients. Therefore, therapy should be directed at tight biochemical control aimed at restoring life expectancy to normal, reversing associated morbidity and alleviating symptoms while preserving pituitary function and controlling tumour growth. An important therapeutic issue is the distinction between remission and cure.[9] Remission refers to inactive disease as defined by a reduction in IGF-1 levels to within the age-adjusted range.[10] Cure is only recognized when neuroregulation of GH secretion is also restored, as documented by the attainment of normal GH suppression after a glucose load.[10]

Surgery

Establishment of a modern definition for tight biochemical control has led to a re-evaluation of the efficacy of surgery in the management of acromegaly. Surgery offers the only chance of cure and is still a first-line treatment in most centres; however, a significant number of patients do not achieve remission or cure with surgery alone. The efficacy of surgery is dependent on surgical experience and tumour size and invasiveness. In the best centres, remission rates for microadenomas of 80–90% have been reported.[11] However, even in the most experienced hands, remission for macroadenomas is achieved in only 50%.[11] When surgery is not carried out by a specialist pituitary surgeon, remission rates are far lower – approximately 40% for microadenomas and 10% for macroadenomas.[12] Complications of surgery include new hypopituitarism in 5–20%, permanent diabetes insipidus in 2–8% and cerebrospinal fluid leak in 2%.[4,5,13]

Radiotherapy

Radiotherapy effectively controls tumour growth in approximately 90% of patients with acromegaly.[14] Although radiotherapy also offers a chance of biochemical remission, this is achieved in the minority and only after several years. In a meta-analysis of 13 studies, IGF-1 was normalized in only 36% of patients with acromegaly following 5- to 14-year follow up.[15] Remission rates increase with time: in one study, increasing from <30% of subjects within 6 years of receiving radiotherapy to 70% of patients more than 6 years after radiotherapy.[16] Therefore, radiotherapy must be combined with effective medical therapy to control interim disease activity.

Radiotherapy is associated with significant morbidity. New anterior pituitary dysfunction develops in 30–50% of patients 5 years after conventional radiotherapy, with gonadotrophin secretion most frequently affected.[16,17] Other complications of radiotherapy include optic neuritis, neuropsychological changes and development of meningiomas and gliomas.[18] One recent study reported an increased mortality rate in irradiated patients than in non-irradiated patients with acromegaly.[19] The increase in mortality was predominantly from cerebrovascular disease and was independent of GH and IGF-1 concentration, tumour size or deficits in other pituitary axes.[19] This centre has also reported an increased risk of cerebrovascular disease in patients with hypopituitarism treated with radiotherapy.[20] In summary, a significant proportion of patients with acromegaly do not achieve remission with radiotherapy, and treatment is associated with significant morbidity.

The development of stereotactic radiotherapy represents an improvement in patient acceptability as a total dose is

delivered in one session, as opposed to conventional radiotherapy, which is given in 30 fractions. Stereotactic radiotherapy also has the advantage of targeting a necrotizing radiation dose at the tumour with high precision, with little radiation to the surrounding tissues, potentially reducing side-effects. However, there have been no head-to-head studies comparing stereotactic radiotherapy with conventional radiotherapy, and long-term follow up is limited.[11] Available data are insufficient to determine whether there is a significant difference in efficacy and safety between conventional and stereotactic radiotherapy.

Medical therapy

The role of medical therapy in acromegaly has expanded greatly over the past 20 years. In 1980, the nonselective dopamine agonist bromocriptine was the only pharmacologic therapy available. Octreotide, which was introduced for clinical treatment in the early 1980s, heralded the modern era of pharmacological treatment. Subsequent development of depot somatostatin analogues, first octreotide LAR and subsequently lanreotide SR and then lanreotide autogel, has markedly improved patient tolerability and acceptability of somatostatin analogue therapy. The selective dopamine agonist cabergoline appears to have greater efficacy than bromocriptine in acromegaly. Pegvisomant, a GH receptor antagonist, is the latest pharmacologic agent developed to treat acromegaly. The increasing availability and greater tolerability and efficacy of medical therapy has resulted in medical therapy assuming an increasingly prominent role in the management of acromegaly.

Somatostatin analogues

Somatostatin analogues can no longer be thought of as 'new', having been used to treat acromegaly for more than 20 years. However, they remain the mainstay of medical therapy for acromegaly. Native somatostatin reduces GH secretion from the anterior pituitary by binding to somatostatin receptors, of which five subtypes have been identified (sst_{1-5}). Two somatostatin analogues are currently available for clinical use – octreotide and lanreotide. Both exert their major effect through binding to sst_2, which they bind to with greater affinity than native somatostatin and which are expressed more frequently in GH-secreting pituitary tumours.[21] The presence of sst_2 in the tumour correlates with clinical efficacy.[22]

It was necessary to give octreotide t.i.d. to achieve effective biochemical control.[23] The development of depot preparations has now supplanted the use of s.c. octreotide. Incorporation of octreotide into microspheres of biodegradable polymer forms the basis of the depot preparation octreotide LAR, which is given intramuscularly every 28 days. Lanreotide was initially available in depot formulation as lanreotide SR, requiring administration every 7–14 days. In 2004, lanreotide autogel, which is given by deep s.c. injection every 28 days, was released in Australia. Depot preparations result in improved patient compliance and acceptability but may also improve efficacy because of the stable and continuous drug levels they provide.

Long-term studies show that depot somatostatin analogues provide good control in acromegaly, with achievement of biochemical targets in ~60% of patients (Table 1). In a recent meta-analysis, the remission rate was reported to be slightly higher with octreotide LAR (~65%) than with lanreotide SR (~50%).[30] However, as reported by Freda, caution should be exercised in comparing studies of the two analogues because of differences in patient selection.[30] Ninety per cent of patients in the trials of octreotide LAR were preselected for octreotide responsiveness compared with 10% in the trials of lanreotide SR. Given that both agents have a similar mechanism of action and selectivity for sst_2, they are likely to have a similar efficacy. The efficacy of lanreotide autogel is similar to that of lanreotide SR.[31]

Both the depot somatostatin analogues reduce tumour mass in approximately 30% of patients with acromegaly,

Table 1 Major trials of depot somatostatin analogues in acromegaly

Somatostatin analogue	Number of subjects	Duration (months)	Normal IGF-1 (% of subjects)	GH <2.5 ng/mL (% of subjects)[†]	Tumour shrinkage (%)[‡]
Octreotide LAR[24]	14	18	64	64[§]	36
Octreotide LAR[25]	151	12	66	70	NA
Octreotide LAR[26]	110	48	75	72	46
Lanreotide SR[27]	22	36	63	27	15
Lanreotide SR[28]	118	24	63	77	9
Lanreotide autogel[29]	92	24	65	63	39

[†]2.5 ng/mL ≈ 7.5 mU/L.

[‡]Percentage of patients who had reduction in tumour size on somatostatin analogue.

[§]<2 ng/mL (6 mU/L).

GH, growth hormone; IGF-1, insulin-like growth factor-1; NA, not assessed.

with tumour shrinkage by 20–50% (Table 1). Somatostatin analogues rapidly reduce symptoms of acromegaly, including headache, paraesthesia, muscle weakness, perspiration and soft tissue swelling. Somatostatin analogues also improve the cardiorespiratory comorbidities associated with acromegaly, reducing left ventricular mass[32] and improving sleep apnoea.[33] The effect of somatostatin analogues on glucose homeostasis is minor and variable and is dependent on glycaemic status before treatment. Improvement tends to occur in those with impaired glucose tolerance, whereas a mild deterioration may occur in those without impaired glucose tolerance.[23]

Somatostatin analogues are generally well tolerated. The most common side-effects are gastrointestinal symptoms such as diarrhoea, abdominal discomfort and nausea. Early side-effects occur in approximately 50% of patients but improve with time and generally persist in <10% of patients.[30] Gallstones develop in 20–30% of patients on somatostatin analogues, influenced by dietary and racial factors, and can be managed similarly to gallstones in the general population.[34] Somatostatin analogues are discontinued in <5% of cases, usually because of gastrointestinal side-effects.[30]

In summary, somatostatin analogues are effective drugs for the treatment of acromegaly. They achieve adequate biochemical control in the majority, control tumour growth and/or induce tumour shrinkage, provide symptomatic relief and improve the comorbidities associated with acromegaly. They are generally well tolerated, particularly when prescribed as depot preparations. Because of their wide-ranging benefits, somatostatin analogues play a major role in the management of acromegaly. However, the cost of somatostatin analogues is considerable at approximately $20 000 per annum, and many patients will require treatment for decades. In Australia, somatostatin analogues receive a Section 100 listing and the cost is borne by the Commonwealth Government.

Dopamine receptor agonists

Dopamine agonists have a limited role in the management of acromegaly. Dopamine receptors are widely distributed in the central nervous system and the gastrointestinal tract and exist as two subtypes, D1 and D2, with the D2 subtype mediating pituitary function. Bromocriptine (a nonselective dopamine agonist) was the first dopamine agonist introduced for the treatment of acromegaly. More recently, several D2-selective agonists have been introduced, including cabergoline, with which there has been the greatest experience worldwide. Cabergoline is approved for the therapy of prolactinoma but not acromegaly in Australasia. Dopamine agonists have the advantage of oral administration and are inexpensive when compared with other medical therapies for acromegaly.

Bromocriptine is rarely effective in acromegaly. A meta-analysis of 31 studies of bromocriptine revealed that IGF-1 is normalized in only 10% of patients.[35] Cabergoline appears to be more effective. The efficacy of dopamine agonists is greater in tumours that cosecrete prolactin. In the largest study, cabergoline normalized IGF-1 in approximately 50% of patients with tumours that cosecrete prolactin and 35% of pure GH-secreting tumours.[36] Tumour shrinkage was seen in 13 of 21 patients and was generally between 20 and 50%.[36] However, in another study of pure GH-secreting tumours, cabergoline failed to normalize IGF-1 in any patient.[37] Because of increased selectivity for D2 receptors, thus avoiding activation of central D1 receptors, cabergoline is better tolerated than bromocriptine and this may contribute to its greater efficacy. The overall data suggest that cabergoline is effective in tumours that cosecrete prolactin and should be trialled first in this situation. Its place is adjunctive for patients with pure GH-secreting adenoma, where it may provide control in patients left with mild residual disease activity after other therapies.

GH receptor antagonists

Pegvisomant is the latest and most exciting development in the treatment of acromegaly. It is likely to play a major adjunctive role in the management of patients who are not effectively treated with all other therapies. Pegvisomant is an analogue of GH, genetically engineered to prevent dimerization of the GH receptor, an event necessary for cellular activation.[38] It is conjugated with polyethylene glycol to reduce renal clearance and immunogenecity.[38] As pegvisomant does not lead to a reduction in GH secretion, IGF-1 levels must be used to assess efficacy of treatment.

In a large, multicentre randomized controlled study, pegvisomant normalized IGF-1 and improved symptoms over 12 weeks in a dose-dependent manner.[39] Longer term data from 160 patients receiving up to 18 months of open treatment confirm the efficacy of pegvisomant, with 97% of patients achieving a normal serum IGF-1.[40] A twofold increase in GH was observed during treatment.[40] Although there are no trials directly comparing pegvisomant with other medical agents, many subjects in the above studies had previously failed other medical therapy.[39,40] Therefore, these data indicate that pegvisomant is more effective than other medical therapies in achieving a normal serum IGF-1. Pegvisomant also results in a greater improvement in insulin sensitivity than somatostatin analogue therapy.[41]

Pegvisomant is well tolerated and safe. It may cause hepatic dysfunction, but this is rare and reversible.[40]

Concern has been raised as to whether the increase in GH may represent tumour growth, as pegvisomant does not act directly on the tumour. Although no significant increase in tumour size was observed over 12 months, longer term follow-up studies are required to ascertain whether the tumour growth history is affected by treatment.[40]

Pegvisomant is an important addition to drug treatment in acromegaly. Despite being the most efficacious, it is unlikely to claim a place as primary treatment because it exerts control by blocking hormone action rather than acting on the tumour.[42] Until further evidence is at hand, pegvisomant should be used to provide biochemical control in conjunction with other therapy directed at the tumour, either a somatostatin analogue or radiotherapy. Pegvisomant has been approved for use in the USA and the European Union for several years and has just been registered in Australia. The cost of pegvisomant will have an effect on its availability and affordability in Australasia, as for most patients it can cost two to four times that of somatostatin analogues, depending on the doses used. Pegvisomant is not listed under the Pharmaceutical Benefit Scheme in Australia.

Modern management of acromegaly

The success of medical therapy with prolactinomas has supplanted surgery as first-line therapy and offers hope that equally effective treatments will find a similar place in the management of acromegaly. Although medical therapy does not offer a chance of cure, it offers the potential to achieve biochemical control of acromegaly, with minimal side-effects (Table 2). Surgical resection is still used as first-line treatment for acromegaly in most centres. However, a significant number of patients will require additional therapy to achieve biochemical control, particularly those with large or invasive tumours.

The question of whether somatostatin analogues can be considered as primary treatment was first raised by a study in which octreotide was as effective in a group of untreated patients as in a group previously treated with surgery and/or radiotherapy.[43] The experience with lanreotide SR is similar.[28] However, in neither study were the patients randomized; therefore, the results may have been affected by selection bias. Despite this caveat, these observations call for a reappraisal of the current practice of surgery regardless of the likelihood of cure, and support the use of somatostatin analogue therapy as primary treatment in some patients, particularly when the likelihood of surgical cure is low. A prospective, randomized, multicentre study comparing primary treatment with octreotide LAR versus surgery is currently in progress.

A proposed algorithm for the management of acromegaly is shown in Figure 1. Where a GH-secreting adenoma is small and the chance of surgical success is high, surgery is recommended as first-line therapy where appropriate neurosurgical expertise is available. Primary somatostatin analogue treatment is a strong alternative if surgery is contraindicated or postponed because of individual patient requirements. Where the tumour is large and/or invasive and the chance of surgical remission is low, somatostatin analogues should be trialed as primary therapy. This allows time to tailor long-term management around an individual patient's responsiveness and requirements. If primary somatostatin analogue therapy is well tolerated, biochemical remission is achieved and tumour growth is arrested or reversed, therapy can be continued indefinitely. If somatostatin analogue therapy does not provide effective control, surgery should be reconsidered. Even if it does not induce remission, the debulking of the tumour improves biochemical control of acromegaly by somatostatin analogues.[44] Debulking surgery is indicated as primary therapy when there is a high risk of visual field loss from suprasellar extension of a tumour and optic chiasmal compression.

A significant number of patients have persistent acromegaly despite surgery and somatostatin analogue therapy. An algorithm for management of these patients is depicted in Figure 2. If pegvisomant is available, we

Table 2 Efficacy of therapies for acromegaly

	Normal IGF-1 (% of patients)	Control of tumour growth	Potential adverse events
Surgery	Microadenomas (40–80), macroadenomas (10–50)	Most effective therapy to reduce tumour size	Hypopituitarism, diabetes insipidus, CSF leak or visual loss
Radiotherapy	30–40 (after 5–15 years)	Prevent tumour growth in 90%, shrinkage in most	High risk of hypopituitarism, possible increase in CVA
Somatostatin analogues	50–60	Prevent tumour growth in most, shrinkage in 30%	Gastrointestinal symptoms: bloating, abdominal pain, gallstones
Dopamine agonists	10–20, 40 (cosecrete prolactin)	Minimal effect on tumour growth	Nausea and postural hypotension, less common with cabergoline
Pegvisomant	95	No effect on tumour growth	Small risk of hepatotoxicity, long-term risk profile unknown

CSF, cerebrospinal fluid; CVA, cerebrovascular accident; IGF-1, insulin-like growth factor-1.

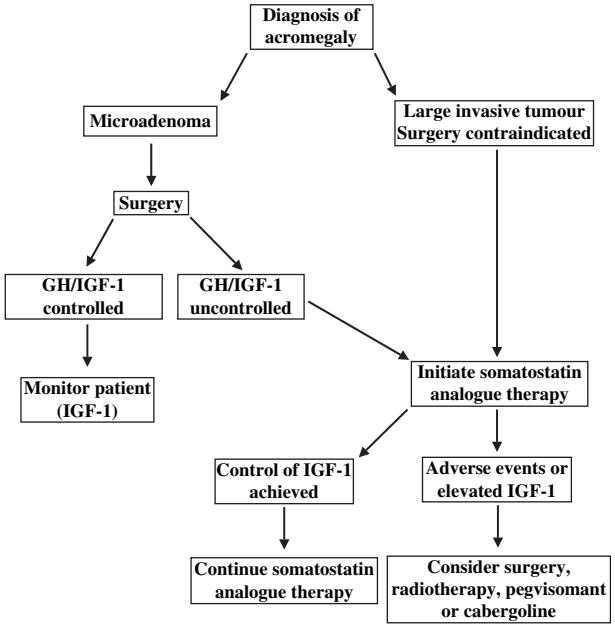

Figure 1 Proposed treatment algorithm for initial management of acromegaly. GH, growth hormone; IGF-1, insulin-like growth factor-1.

recommend it as secondary medical therapy in most patients. Where residual disease is mild, cabergoline should be trialled first. If pegvisomant is unavailable or if there is a large residual tumour, radiotherapy is recommended to achieve long-term control of persistent disease and a reduction in tumour mass. Radiotherapy is not recommended as secondary treatment after failed surgery, which has been past practice. Radiotherapy has a diminishing role in the multidisciplinary management of acromegaly, with its place supplanted by medical therapy, which provides faster biochemical control with lower morbidity.

Future directions

Ongoing drug development has centred on the development of somatostatin analogues with greater efficacy than those presently in use. Greater than one-third of patients with acromegaly do not achieve adequate biochemical control with octreotide or lanreotide. This is likely to be related to variability in tumour expression patterns of somatostatin receptor subtypes. Both octreotide and lanreotide reduce GH secretion primarily through binding to sst_2.[21] New somatostatin analogues are currently under development, with a broader pattern of sst activation, including effects mediated through sst_5, which also inhibits GH secretion. These agents have the potential of enhanced efficacy and potency from coactivation of biologically active sst controlling GH release.

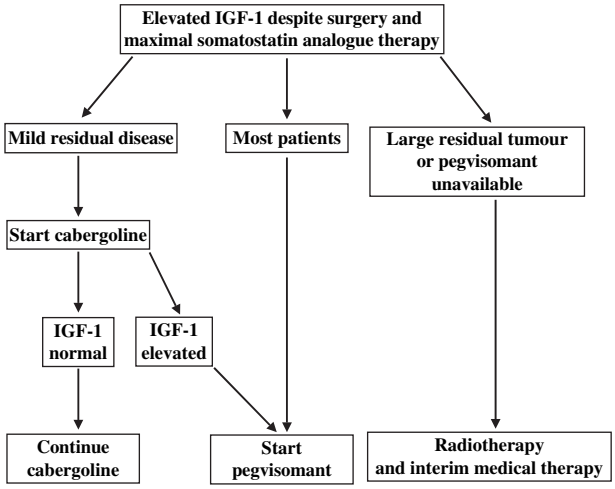

Figure 2 Proposed treatment algorithm for management of patients with persistent acromegaly, despite surgery and maximal somatostatin analogue therapy. IGF-1, insulin-like growth factor-1.

BIM-23244 and SOM230 are two new somatostatin analogues with high affinity to both sst_2 and sst_5. Both appear to be effective in a greater range of tumours than octreotide; however, they do not have greater efficacy in tumours that are 'octreotide responsive'.[22,45,46] As sst_5 receptors are widely distributed in the gastrointestinal tract, there are concerns that these agents may cause more gastrointestinal side-effects and exert detrimental effects on insulin secretion. Another analogue, BIM-23A387, is a hybrid 'dopastatin' molecule, with ability to bind and activate the sst_2 and D2 receptor. *In vitro*, BIM-23A387 has greater potency than specific sst_2 agonists.[47] The place of these 'newer' somatostatin analogues in clinical practice remains to be established.

Conclusions

The twenty-first century has ushered exciting advances in the management of acromegaly. A greater understanding of the importance of biochemical control, at a time when treatment options are expanding, calls for a reappraisal of the most appropriate therapeutic approach. An important target of acromegaly management is the attainment of tight biochemical control, which equates to a GH of <2.5 ng/mL (~7.5 mU/L) and an IGF-1 within the age-adjusted normal range. This has been made increasingly possible by major drug developments, based on an understanding of neuroendocrine physiology. Although medical therapy does not offer the chance of cure, it allows the possibility of biochemical control of acromegaly without the risk of impairing other pituitary function. Randomized controlled trials currently underway will provide insight into the appropriate patients in whom primary medical

therapy is most likely to be of benefit. Although acromegaly remains a difficult disease to manage, the outcome for patients with acromegaly is likely to improve. The availability of more effective and better tolerated therapies offers greater flexibility and the potential to individualize patient treatment.

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