

Clinical applications of somatostatin analogs for growth hormone-secreting pituitary adenomas

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Abstract: Excessive growth hormone (GH) is usually secreted by GH-secreting pituitary adenomas and causes gigantism in juveniles or acromegaly in adults. The clinical complications involving cardiovascular, respiratory, and metabolic systems lead to elevated morbidity in acromegaly. Control of serum GH and insulin-like growth factor (IGF) 1 hypersecretion by surgery or pharmacotherapy can decrease morbidity. Current pharmacotherapy includes somatostatin analogs (SAs) and GH receptor antagonist; the former consists of lanreotide Autogel (ATG) and octreotide long-acting release (LAR), and the latter refers to pegvisomant. As primary medical therapy, lanreotide ATG and octreotide LAR can be supplied in a long-lasting formulation to achieve biochemical control of GH and IGF-1 by subcutaneous injection every 4–6 weeks. Lanreotide ATG and octreotide LAR provide an effective medical treatment, whether as a primary or secondary therapy, for the treatment of GH-secreting pituitary adenoma; however, to maximize benefits with the least cost, several points should be emphasized before the application of SAs. A comprehensive assessment, especially of the observation of clinical predictors and preselection of SA treatment, should be completed in advance. A treatment process lasting at least 3 months should be implemented to achieve a long-term stable blood concentration. More satisfactory surgical outcomes for noninvasive macroadenomas treated with presurgical SA may be achieved, although controversy of such adjuvant therapy exists. Combination of SA and pegvisomant or cabergoline shows advantages in some specific cases. Thus, an individual treatment program should be established for each patient under a full evaluation of the risks and benefits.

Keywords: GH-secreting pituitary adenoma, somatostatin analogs, lanreotide ATG, octreotide LAR, growth hormone, insulin-like growth factor 1

Introduction

Pituitary adenoma accounts for 15% of primary intracranial tumors.¹ Growth hormone (GH)-secreting pituitary adenoma had a World Health Organization 2000-standardized incidence rate of 0.34 per 100,000. GH-secreting pituitary adenoma is the only type of adenoma that shows a male-dominant tendency, although the difference due to sex is not significant.² Excessive GH secretion can cause gigantism in juveniles, because of the active epiphyseal growth plates that allow linear growth, or acromegaly in adults.³ The data of incidence, clinical presentations, and treatment strategy for patients with gigantism is limited, owing to its lower incidence rate relative to that of acromegaly;^{3,4} however, similar organomegaly and deteriorating glucose tolerance have been found in follow-up patients⁵ with either acromegaly or gigantism.⁶ Recent studies have shown that therapy for acromegaly was also successful and safe in patients with gigantism.^{3,6–8}

Thus, in this review, we mainly summarize the clinical application of somatostatin analogs (SAs) for acromegaly, with the related data of gigantism being discussed in the last part of this review.

Background

Clinical manifestation

Acromegaly and gigantism usually manifest as coarsened facial features and hypertrophy of hands, feet, and soft tissue.⁹ The characteristic clinical manifestations mainly derive from local mass effects and biological function of excessive secreted GH. First, the compression of local nerves causes temporal hemianopia of one or both eyes, ophthalmoplegia, and ptosis.¹⁰ Further, the elevated intrasellar pressure could shut down the hypophyseal portal vein, which carries regulatory hormones from the hypothalamus, therefore leading to hypopituitarism and moderate hyperprolactinemia.¹¹ Second, the excessive secretion of GH and insulin-like growth factor (IGF) 1 will lead to severe complications in the cardiovascular, respiratory, metabolic, skeletal, and integumentary systems, which subsequently increases the risk of death significantly.¹² Cardiovascular complications, especially myocardial infarction, are the most common cause of death, while malignancy and cerebrovascular events occupy the second and third most common causes of mortality, respectively.¹³ Although the biologic changes are usually more concerning, the mass effects of GH-secreting pituitary adenoma should not be ignored. Temporal hemianopia, ophthalmoplegia, ptosis, and hypopituitarism affect the quality of life in patients with pituitary adenoma to a variable extent, while hemorrhage in giant pituitary adenoma can lead to acute pituitary apoplexy, which is a life-threatening condition.

Treatment goals and strategies

A previous study has indicated that GH <2.5 ng/mL, younger age, and shorter duration of disease are the independent determinants of longer survival,¹ so the indication of medical intervention should be confirmed after diagnosis.¹⁴ Sometimes, the serum GH and IGF-1 show a divergent relationship;¹⁵ hence, if both the random serum GH <2.5 ng/mL and IGF-1 normalization for age and sex can be achieved, patients can be expected to have nearly the same duration of life as unaffected persons.¹⁶

The current therapies of GH-secreting pituitary adenoma are surgery, medical treatment, and radiotherapy.¹⁴ The main aim of these approaches is to remove the mass that compresses its surroundings and to normalize serum GH and IGF-1 levels.^{12,16} Although different treatments have their specific

advantages and disadvantages, the ultimate goal of the treatment is to reduce the mortality and morbidity in acromegaly and gigantism patients. Transsphenoidal surgery is an optimal choice for microadenomas and noninvasive macroadenomas, especially for the resolution of compression. The biological control rates of GH and IGF-1 can reach 75%–95% in microadenomas and 40%–68% in noninvasive macroadenomas.¹⁴ Patients with a tumor less than 2 cm and random serum GH level less than 50 ng/mL show higher remission rates after surgery;¹⁶ however, about 40%–60% of macroadenomas are unable to be cured by surgery alone because of the invasion to cavernous sinus or third ventricle.¹⁴ Although complete excision of such macroadenomas is impossible, surgical debulking could enhance the effect of SA.^{17,18} For medical therapy, SA, GH receptor antagonist (GHRA), and dopamine agonist (DA) are available. SAs are the strongly recommended medical treatment for GH-secreting pituitary adenoma when surgery fails to achieve GH and IGF-1 normalization.¹⁴ Radiation therapy for GH-secreting pituitary adenoma is recommended as a third-line treatment to control excessive GH or IGF-1 when surgery and medical treatment are unsuccessful.¹⁴ The main limitation of radiation therapy is safety, considering the high occurrence rate of hypopituitarism.¹⁹

Overview of medical treatment

Patients with GH-secreting pituitary adenoma receiving SA treatment for more than 3 months show a reduced tumor volume and normalized serum GH and IGF-1.²⁰ There are two efficient, long-lasting formulations of SA, octreotide long-acting release (LAR) and lanreotide Autogel ([ATG]; Ipsen, Paris, France), which replace lanreotide slow release (SR) because of their higher rate of response.^{21–25} They are equivalent in the control of biological markers and tumor volume.^{26,27} Although GHRA shows high efficacy in improving quality of life and controlling IGF-1, tumor shrinkages are not observed in most patients.²⁸ Also, the guidelines of Melmed et al limit the strong recommendation of GHRA in the case of persistently elevated IGF-1 despite a maximal dose of SA treatment.¹⁴ Recent data show that a combination of SA and GHRA is effective and can greatly reduce the costs of medical therapy.^{29,30} As per the findings of Abs et al in 1998, there was limited effect in monotherapy with cabergoline for acromegaly.³¹ A recent meta-analysis, however, conducted by Sandret et al, who systematically reviewed all trials of cabergoline therapy for acromegaly, suggested that cabergoline could achieve better results than expected, either alone or in combination with SA.³²

In this review, we will focus on the clinical predictors, preselection of SA, and the benefits from the stable blood concentration. The controversy of presurgical SA treatment and the different strategies of primary or secondary medical treatment will also be discussed (Table 1).

Optimization of SA treatment

Clinical predictors of medical treatment

As mentioned above, it is important to reduce both GH and IGF-1 to normal levels;¹⁶ however, patients with GH-secreting pituitary adenoma show different susceptibilities to SA treatment. The full response to a 12-month SA treatment includes control of GH/IGF-1 and more than 20% tumor shrinkage in primary treatment or no tumor remnant on magnetic resonance imaging, while a partial response means that a more than 50% decrease of GH and/or failure to control IGF-1 levels with or without more than 20% tumor shrinkage is obtained (Table 2).³³ Taking the cost of SA treatment into account, it is necessary to access the benefit before the treatment. Clinical predictors of SA treatment that are already known include tumor size, serum GH before treatment, and the density of the somatostatin receptor (SSTR).^{34–36} Related studies have shown that, in patients with serum GH >16.7 ng/mL or 20 ng/mL, SA treatment is unsatisfactory for GH/IGF-1 control and tumor shrinkage.^{34,35} In the study by Colao et al, small, noninvasive tumor with low serum GH demonstrated a better response to lanreotide ATG.³⁷ According to the results of molecular biological researches, SSTRs, on which somatostatin binds, have five subtypes, of which SSTR 2 and 5 are predominantly expressed on the cell membrane of GH-secreting pituitary tumor cells.³⁸ High-density SSTR distribution on the tumor cell may result in a promising response to SA treatment;^{36,38} however, Bertherat et al showed that loss of SSTR could not explain the continued partial suppression of GH induced by SA and that the density of SSTR was poorly related to SA

Table 2 Definition of response to somatostatin analog treatment (12 months)

	Biochemical response	Tumor response
Full response	Random serum GH <2.5 ng/mL and a normal IGF-1 for age and sex	>20% tumor shrinkage in patients with primary treatment; stabilization of tumor remnant or no recurrence in patients treated with secondary treatment
Partial response	Significant decrease (>50%) of GH level and/or failure to control IGF-1 levels	With or without tumor shrinkage
Resistance	Nonsignificant decrease of GH and IGF-1 levels with no achievement of control	No tumor shrinkage in patients treated first-line or increase in tumor size in any patient

Notes: OGTT is not recommended for monitoring therapeutic response during SA treatment. Data from Melmed et al.¹⁴ Republished with modification in full response of Biochemical response and with permission of Endocrine Society, from Resistance to somatostatin analogs in acromegaly. Colao A, Auriemma RS, Lombardi G, Pivonello R. 2011;32(2):247–271.³³ Permission conveyed through Copyright Clearance Center, Inc. **Abbreviations:** GH, growth hormone; IGF-1, insulin-like growth factor 1; OGTT, oral glucose tolerance test.

treatment *in vivo*.³⁹ In other words, factors apart from those mentioned also play a role in influencing SA treatment results. Several factors have been found to affect susceptibility to lanreotide and octreotide. For example, in female patients with hypogonadism, oral estrogens together with SA could facilitate better IGF-1 reduction compared with SA monotherapy.⁴⁰ In addition to this, elderly people who show obvious cardiovascular or respiratory complications at diagnosis are more sensitive to SA treatment.⁴¹

Preselection before medical treatment

With different responses to SA treatment, patients with GH-secreting pituitary adenoma need preselection before the medical treatment. To predict the long-term response to SA treatment in patients with GH-secreting pituitary adenoma, the acute octreotide suppression test and ¹¹¹In-pentetreotide scintigraphy are applied clinically.^{42–44} The acute octreotide test involves the use of subcutaneous Sandostatina (Sandoz, Milano, Italy) 50/100 µg to suppress the secretion of GH. Serum GH is assayed before (30 minutes, 15 minutes, 5 minutes) and after (hourly intervals for 6 hours) the sandostatina treatment.⁴² In the earliest study of the acute octreotide test, Lamberts et al found a close relationship between the mean serum GH measured 2–6 hours after a subcutaneous 50 µg sandostatina administration and the mean 24-hour serum GH after a 96-week sandostatina treatment.⁴⁴ Therefore, they hypothesized that the measurement of serum GH after an acute administration of 50 µg sandostatina might be a good method for dose adjustment;⁴⁴ however, the results differed in other studies. Colao et al, in 1996, conducted a similar study with octreotide subcutaneous 100 µg for suppression, and the

Table 1 Main content of this review

Optimization of somatostatin analog treatment	Clinical predictor of medical treatment Preselection before medical treatment Achieve long-term stable blood concentration Clinical use in presurgical period and impact on surgery Comparison of lanreotide Autogel [®] and octreotide long-acting release
Different strategies	Primary or secondary therapy
Drug combinations	Pegvisomant; cabergoline
New somatostatin analogs	
Treatment of gigantism	

Note: [®]lpsen, Paris, France.

data showed that the acute test could not determine whether the patients might respond to the long-term treatment or not.⁴² With the use of depot long-acting somatostatin in clinic, the current standard for judging the response to SA treatment is stricter, and the value of the acute octreotide suppression test in predicting the long-term SA treatment response needs reassessment. Furthermore the criterion for the acute octreotide test response affects the results. In a study by Karavitaki, the data showed that, when the criterion of GH <2 ng/mL was adopted in the acute octreotide test, the sensitivity, specificity, positive predictive value, and negative predictive value of safe serum GH were 92%, 67%, 92%, and 67%, respectively, for the 6-month lanreotide therapy and 100%, 80%, 94%, and 100%, respectively, for the 6-month octreotide LAR therapy;⁴² however, the results of IGF-1 normalization were not satisfied.⁴³ In a meta-analysis by Freda et al, the authors summarized the efficacy of two SA treatments and found that preselection was a positive predictor for IGF-1 and tumor shrinkage but not for serum GH.⁴⁵ Although the abovementioned studies demonstrated varying results, the acute octreotide test showed its advantages in the prediction of long-acting SA treatment response, especially for sensitivity, which means that patients who respond to the acute octreotide test would be more likely to benefit from long-acting SA treatment.

In the preselection procedure using ¹¹¹In-pentetreotide scintigraphy, related data show discrepant results.^{42,46–48} Plöckinger et al found that ¹¹¹In-pentetreotide could be taken by pituitary adenoma cells regardless of the immunohistological subtypes,⁴⁶ although the pentetreotide was expected to combine with SSTR. However, the small numbers of patients, lack of long-term follow-up, and failure to fulfill the current criterion of response to SA treatment in the earlier study means that preselection by ¹¹¹In-pentetreotide scintigraphy is not widely used.

Achieving a long-term stable blood concentration

Lanreotide ATG itself is a sustained-release profile, lanreotide ATG shows a half-life of 22 days and residence time of 30–32 days for a 40/60 mg single dose.⁴⁹ The mean steady-state serum concentration of 3.82, 5.69, 7.69 ng/mL were obtained in about 84 days following four doses of 60, 90, and 120 mg ATG every 4 weeks, respectively, in patients with acromegaly.⁵⁰ For octreotide LAR, the time to reach maximum drug concentration was 22 days for octreotide 20 mg and 12.6 days for 60 mg, while the steady state of long-acting octreotide 20 mg after three doses with 28-day intervals showed a mean concentration, minimum concentration, and maximum concentration of 1,216, 1,065, and 1,585 pg/mL, respectively, and that the

concentration was maintained at a consistent level during the dose intervals.⁵¹ Thus, to obtain a maximal and lasting clinical benefit, the SA treatment schedule of at least three to four doses with a 4-week interval is suggested. Such a treatment schedule was adopted in earlier studies concerning the effect of SA. Furthermore, longer treatment duration may bring higher response rates and better symptomatic improvements as outlined in the guidelines of Melmed et al.¹⁴ In recent studies, the observation of serum GH, IGF-1, and tumor shrinkage was performed after a long-term treatment of no less than 12 months,^{22,52,53} in which a better biochemical marker response and more obvious tumor shrinkage was achieved compared with after a 3-month treatment.^{21,53} Besides the increased percentage of patients who achieved safe serum GH and normalized IGF-1, the vascular, cardiac, and sleep parameters were improved with 6-month ATG treatment.⁵⁴

Clinical use in presurgical period and impact on surgery

The main purpose of presurgical application of SA treatment is to remit the complications involving cardiovascular, respiratory, and, probably, metabolic systems to further decrease the anesthetic and perioperative risks^{54,55} and to decrease serum GH and IGF-1 levels and reduce tumor volume, which possibly leads to higher rates of total tumor resection.¹⁴ Cardiovascular complications are the major cause of acromegaly morbidity.¹² Longer duration of disease activity and older age may lead to a higher risk during the perioperative period. Therefore, though such negative events were not proven, in the study of Seidman et al, to be markedly higher in active acromegaly than in controls,⁵⁶ it is still worthwhile to emphasize the benefit of cardiovascular control during and after surgery,⁵⁵ since the presurgical usage of SA has been demonstrated to result in decreased complication rates and shortened durations of hospitalization.⁵⁷ Because of the varied durations of presurgical application of SA among studies,^{55,57,62,64,65,70,78} however, the potential cost benefit needs to be further assessed. The improvements in cardiovascular function could be achieved after a single dose of lanreotide,⁵⁸ whereas, in the study of Annamalai et al, a 6-month treatment might be needed.⁵⁴ As for respiratory complications, which mainly refer to change of lung volumes and the ventilation/perfusion relationship, long-term SA treatment could reduce their occurrence.^{12,14} Nevertheless, the adverse respiratory events caused by intubation difficulty during anesthesia, derived from laryngeal and pharyngeal soft tissue hypertrophy or vocal cord swelling, could not be prevented by presurgical SA treatment.^{55,56} For metabolic complications,

there is no report suggesting that metabolic complications can cause severe perioperative problems in acromegaly, although patients with uncontrolled blood sugar levels were detected in 30% in acromegaly.¹² In a previous report, diabetic patients were shown to be at increased risk for poor wound healing and susceptibility to infection;⁵⁹ therefore, the control of blood sugar might bring benefits for acromegaly patients who are prepared for surgery.⁵⁵ In a study of octreotide by Colao et al, 6-month SA treatment decreased the insulin demand in patients receiving an insulin treatment and normalized the blood glucose in patients taking oral glucose control drugs.⁵⁷ Similar studies of lanreotide were also conducted, and a stable blood glucose status could be achieved.^{60,61}

Controversy persists among neurosurgeons regarding whether presurgical SA treatment could lead to a significant improvement of total resection of radical operation.^{55,57,62–72} Surgery provides the biochemical cure of normalized IGF-1 in 75%–95% of patients with microadenomas and 40%–68% of patients with noninvasive macroadenomas.^{68,73–77} In patients with invasive pituitary adenomas, a partial removal of tumor replaces the radical operation.^{68,74} For microadenomas, the cure rate by surgery is already high, so the presurgical SA treatment increases the cure rate slightly but not significantly.⁶³ For invasive adenomas, although tumor shrinkage was observed in most studies, the long-term biological control of serum GH and IGF-1 levels could not be achieved.⁶⁴ In the study of Mao et al, a higher rate of biochemical cure was observed in patients with presurgical SA treatment in 1–3-month follow-ups;⁷⁸ however, this may have resulted from the cumulative effect of presurgical SA rather than from an actual increase of total resection. Considering the high cure rate of microadenomas by surgery and the difficulties of total resection for invasive macroadenomas, even with presurgical SA treatment, the assumption that a more satisfactory surgical outcome of noninvasive macroadenomas could be achieved through tumor shrinkage resulting from the presurgical SA treatment is reasonable.

Comparison of lanreotide ATG and octreotide LAR

As mentioned in the guidelines of Melmed et al, in well-designed trials, the current long-acting SAs, lanreotide ATG and octreotide LAR, show equivalence in their control of symptoms and no significant difference in their ability to normalize serum GH and IGF-1.¹⁴ Although a number of studies concerning presurgical treatment with lanreotide ATG or octreotide LAR exist, there are few prospective large-scale randomized trials comparing the effects of lanreotide ATG

and octreotide LAR, and thus no definite conclusion has yet been achieved.^{62,64,67,69,70,78} Lanreotide ATG and octreotide LAR may therefore have similar effects in clinic according to the current data.

Different strategies: primary and secondary therapy

Medical treatment with long-acting SA allows for convenient application and shows potential advantages in controlling serum GH and IGF-1 levels; however, the cost–benefit effects of SA treatment should be carefully considered, whether intended as primary or secondary therapy. The indications of SA for acromegaly management recommended in the 2009 guidelines of Melmed et al are as follows: low probability of surgical cure; failure to control serum GH and IGF-1 surgically; and the aim of improving severe perioperative comorbidities before surgery and maintain disease control between each two adjacent administrations of radiation treatment.¹⁴ That is to say, both primary and secondary SA treatments are suggested in appropriate conditions. In the investigation by Giustina et al, the data showed that neurosurgery was the treatment of choice, for microadenomas and macroadenomas with compression to the optic nerve, in most pituitary adenoma centers in the world.⁷⁹ Further, SAs were chosen as the primary treatment in the condition of macroadenomas with lateral extensions.⁷⁹ In this case, both primary SA therapy and secondary SA therapy following surgery debulking were optional.⁸⁰ Increased response percentage of patients with secondary lanreotide was found if more than 75% tumor debulking was achieved.¹⁷ Prospective trials comparing secondary SA treatment following surgery and primary SA treatment are few, although both therapies have been proven effective in the treatment of GH-secreting pituitary adenoma^{17,80}

Drug combinations

As the only GHRA available, pegvisomant has shown its effectiveness in the control of IGF-1.⁸¹ Recent studies have shown that the combination of SA and pegvisomant in patients who could not achieve IGF-1 normalization was safe and aided improved quality of life in acromegaly.^{82–85} Further, the combination of pegvisomant and SA could reduce the dose of SA that is required.⁸⁴ There is, however, no evidence adequate to prove the significant benefits obtained from combination.⁸⁴ In Melmed et al's guidelines, such combination is recommended on the condition that patients are resistant to other treatments.¹⁴ In combination with cabergoline, the combination of SA and cabergoline might provide effective treatment in patients with mixed pituitary adenomas in whom simultaneously elevated

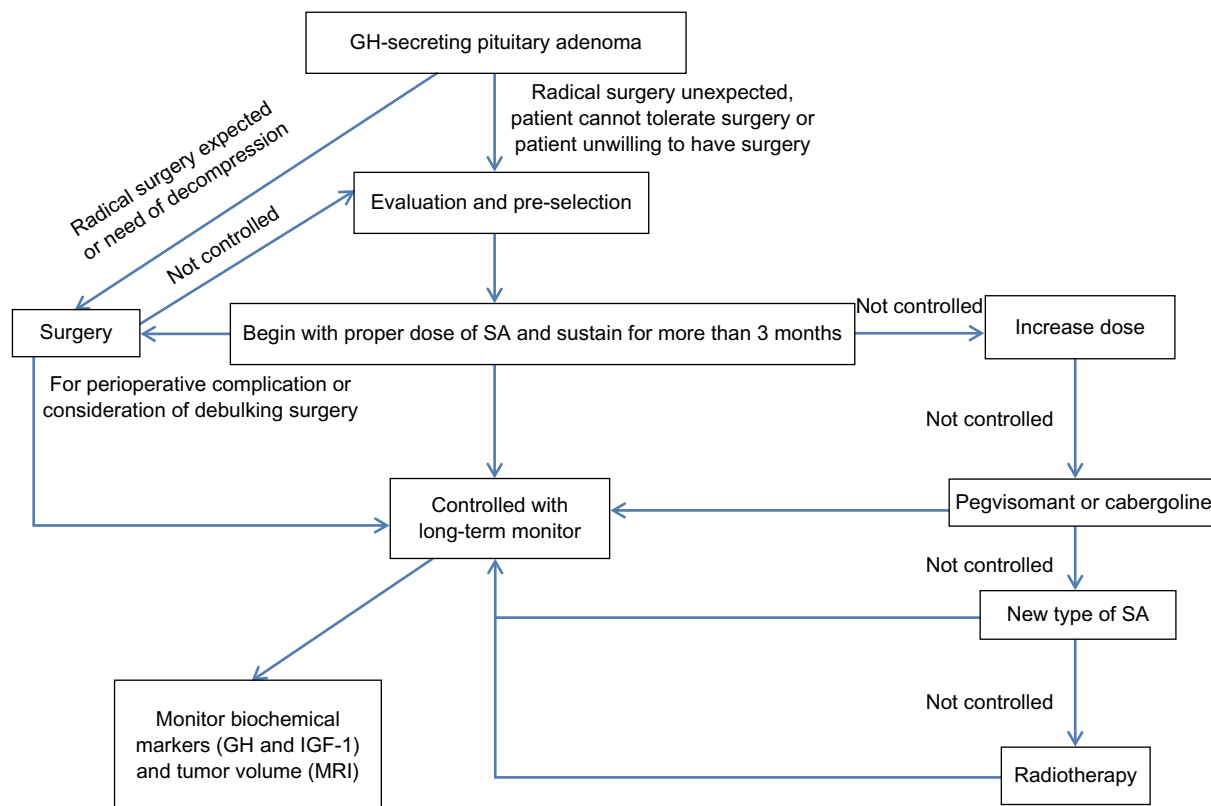


Figure 1 Proposed treatment strategy for patients with acromegaly.

Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; SA, somatostatin analog.

prolactin (PRL) and GH are observed,⁸⁶ while, in patients who are partially responsive to the maximum SA dose, additive therapy with cabergoline could normalize IGF-1 in about half of the patients, including those without prolactinemia.³²

New SAs

Pasireotide, as a new SA,³³ is reported to show high affinity to SSTR 1, 2, 3, and 5.⁸⁷ Therefore, it has the potential to be effective in the control of GH, IGF-1, and tumor volume, as shown in a long-term trial investigating the efficacy and safety of pasireotide in acromegaly (Phase II extension study),⁸⁸ and pasireotide is expected in the treatment of Cushing's disease.⁸⁹ There is, however, no evidence proving that pasireotide is valuable when the tumors are resistant to other SAs, despite its special utility in treating tumors resistant to SSTR 2-preferential analogs, which is owing to its high-affinity binding to SSTR 1, 2, 3, and 5.^{90,91} Dopastatin (BIM23A760) is reported to bind to SSTR 2 and 5 and dopamine D2(DAD2) compound, and somatropin (DG3173) is a novel SA with additional binding to SSTR 4 and low insulin-suppressing activity in preclinical studies; these SAs are therefore expected to be effective and supplementary in the treatment of acromegaly with octreotide and lanreotide.⁹²⁻⁹⁴

SAs in the treatment of gigantism

For the treatment of gigantism, the optimal choices include transsphenoidal surgery, medical therapy, and radiation therapy.³ In the case of microadenomas and well-circumscribed macroadenomas, transsphenoidal surgery may provide a curative effect.⁹⁵ Radiation therapy can induce the normalization of GH, but the rate of hypopituitarism after treatment is high.³ In recent years, the development of long-acting SAs has provided a highly effective method by which to control serum GH and normalize IGF-1.^{6,7} Lanreotide or octreotide as the primary therapy,⁷ or combined with surgery,⁶ are effective and safe for gigantism. However, the numbers of patients were limited in the studies concerning medical treatment of gigantism,⁶⁻⁸ so conclusions concerning the effect of medical treatment for gigantism are still unclear.

Conclusion

Long-acting lanreotide and octreotide provide an effective medical treatment whether as primary or secondary therapy for the treatment of GH-secreting pituitary adenoma. Following the development of therapeutic strategies for GH-secreting pituitary adenoma, better prognosis with higher control rates of serum GH and IGF-1 has been achieved.

Considering, however, the high cost of SA drugs, several points should be considered before medical treatment. A proposed strategy of treatment for patients with acromegaly is summarized in Figure 1. The complete assessment of medical treatment should contain the observation of clinical predictors and preselection, if necessary. To achieve a long-term stable blood concentration, a treatment process of more than 3 months should be implemented. Although controversy regarding presurgical adjuvant therapy exists, more satisfactory surgical outcomes of noninvasive macroadenomas may be achieved. Primary and secondary therapy of SA treatment show no obvious differences with limited data. Thus, in conclusion, a individualized treatment program should be established for each patient after a full evaluation of the risks and benefits to achieve maximum effectiveness with minimum costs.

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Disclosure

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