

Medical Management of Functioning Pituitary Adenoma: An Update

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Abstract

The treatment of functioning pituitary adenoma (FPA) must achieve endocrinological remission as well as tumor size reduction. The first-line treatment of FPA except prolactinoma is transsphenoidal surgery (TSS). Medical treatments and/or radiation will be applied as adjuvant therapies succeeding to TSS. In patients with prolactinoma, dopamine agonists, especially cabergoline, are quite efficient. Dopamine agonists decrease plasma prolactin levels and induce shrinkage in most patients and can be ceased in some of them. In patients with acromegaly, dopamine agonists, somatostatin analogues, and growth hormone receptor antagonist have been used as a monotherapy or the combination, and the high remission rate can be achieved. Pasireotide having high affinity to type 5 somatostatin receptors will be available for the patients presenting resistance against type 2 receptor agonists, such as octreotide and lanreotide. The preceding treatment with somatostatin analogues is beneficial for improving the success rate of TSS. The chimera compounds of somatostatin analogues and dopamine agonists have been investigated. The medical treatments of Cushing's disease are challenging, if TSS is not successful. To suppress ACTH secretion, dopamine agonists and somatostatin analogues have been examined, but neither came to show a sufficient effect. Pasireotide reduces urinary cortisol excretion with a high remission rate. Adrenal enzyme inhibitors (AEIs), such as metyrapone, can inhibit cortisol synthesis from adrenal glands promptly and sufficiently in most of patients. LCI699, a newly developed AEI, is more potent than metyrapone and will be available. We should use available medical treatments for improving the prognosis and quality of life.

Key words: prolactinoma, acromegaly, Cushing's disease, somatostatin analogue, dopamine agonist

Introduction

Pituitary tumors consist of 15% of intracranial tumors and functioning pituitary adenomas account for 30% of all pituitary tumors.¹⁾ The first-line treatment of most functioning pituitary tumors except prolactinoma is the surgical removal, especially transsphenoidal surgery (TSS).²⁾ If the TSS is unsuccessful for controlling the hormone secretion and tumor proliferation, the medical treatment and/or radiation therapy will be necessary.^{2–6)} Since 1990s, several options of medical treatment and radiation delivery have been emerged for treatment of prolactinoma, acromegaly, thyrotropin-secreting pituitary adenoma, and Cushing's disease. Until now, many studies about the efficacy of those treatments have been reported. Most medical options support the treatment after pituitary surgery. In addition, some are efficient

to control the function without surgery. Therefore, this article reviews the medical management of functioning pituitary adenomas. The current medical treatment for functioning pituitary adenoma is summarized in Table 1.

Prolactinoma

About one-third of functioning pituitary adenomas are prolactinomas. The increase in plasma prolactin levels induces amenorrhea/oligomenorrhea, galactorrhea, infertility, impotence, headaches, and visual disturbance.

Most of pituitary adenomas other than prolactinomas are initially treated by surgery. However, the first treatment choice of most prolactinomas is medication rather than surgery.⁷⁾ The surgical management is employed only for patients with optic chiasm compression and progressive visual deficit, for hemorrhagic tumor, or for intolerance of medical treatments.

Table 1 Summary of current medical treatment for functioning pituitary adenoma

	Treatment	Agent	Disadvantage	Remission rate
Prolactinoma	DA	Cabergoline Bromocriptine	Cardiac valve insufficiency* Nausea Orthostatic hypotension Nasal stiffness	70–90% ^{10,12)}
Acromegaly	DA	Cabergoline Bromocriptine	Same as above Same as above	10–40% ²⁷⁾
	SSA	Octreotide Octreotide LAR Lanreotide Autogel	Expensive Nausea Abdominal discomfort Diarrhea Cholelithiasis Insulin inhibition	40–60% ³²⁾
	GRA	Pegvisomant	Liver damage Lipohypertrophy at injection sites	60–90% ^{40,43)}
Cushing's disease				
Pituitary-directed	DA	Cabergoline	Same as above	
	SSA	Octreotide LAR	Same as above	
Adrenal-directed	AEI	Metyrapone Mitotane	Adrenal insufficiency Irreversible adrenal change	20–70% ^{56,57)}

*: observed in patients taking greater than 3 mg cabergoline daily.¹⁷⁾ AEI: adrenal enzyme inhibitor, DA: dopamine agonist, GRA: growth hormone receptor antagonist, SSA: somatostatin analog.

Dopamine receptor agonists

The shrinkage of prolactinoma and the decrease in plasma prolactin levels lead to control the signs and symptoms of hyperprolactinemia. The secretion of prolactin is regulated by dopamine in normal lactotrophs. The medical treatment of prolactinoma is the activation of lactotroph D2 receptors. The activation of D2 receptors induces a decrease in the activity of intracellular signal transduction (adenylate cyclase and cyclic adenosine triphosphate), leading to the decrease in prolactin synthesis and secretion.^{8,9)}

Dopamine agonists such as bromocriptine and cabergoline are usually used for the treatment of micro- and macro-prolactinomas.¹⁰⁾ Bromocriptine, an ergot derivative, is administered once or more daily because of its short action. The initial dose of bromocriptine is 1.25 mg in the evening. Based on plasma prolactin levels, the dose of bromocriptine is increased. The effects of cabergoline are longer than bromocriptine.^{11,12)} Cabergoline is administered once or twice weekly. The dose of cabergoline is 0.25–1 mg each time. Bromocriptine and cabergoline normalize plasma prolactin levels up to 90%.^{10,12)} Both dopamine agonists reduce the size of macroprolactinomas in most of patients.¹⁰⁾ In a study comparing

standard doses of bromocriptine and cabergoline in female patients with prolactinoma, cabergoline was more effective and better tolerated.¹³⁾ Recently, high dose cabergoline has been recommended to achieve high remission rate in patients with macroprolactinomas.¹⁴⁾ Cabergoline is used at up to 12 mg weekly. It has been reported that dopamine agonists can be withdrawn in patients with treatment-responsive prolactinomas.¹⁵⁾ The withdrawal of cabergoline can be tried when the normalization of plasma prolactin levels continues for at least 2 years.¹⁵⁾ Recurrence rates 2–5 years after the withdrawal of cabergoline are greater than 30%.¹⁵⁾

The adverse events of dopamine agonists are nausea, orthostatic hypotension, nasal stuffiness, and depression. It is possible to minimize the side effects by a slow escalation of the dose. The side effects of cabergoline are less frequent than those of bromocriptine.¹⁶⁾ A recent study has reported that cabergoline administration may be associated with cardiac valve disease in patients with Parkinson's disease.¹⁷⁾ The valve insufficiency was reported in patients taking a cumulative dose of cabergoline more than 3 mg daily. The dose is apparently higher than that routinely administered for the treatment

of prolactinomas. However, it will be recommended to perform cardiac echography.¹⁸⁾

Acromegaly

Acromegaly results from excessive growth hormone (GH) secretion from pituitary tumor. In rare patients, ectopic GH releasing hormone (GHRH) production causes acromegaly.^{19,20)} GH-producing pituitary adenoma occurred in about 20% of all pituitary adenomas.²¹⁾ In patients with uncontrolled acromegaly, the increased risk of heart diseases, high morbidities and mortalities have been reported.^{22,23)} The TSS is the first-line treatment in most patients with acromegaly.¹⁾ For the long-term successful management, the combined modality treatments should be often necessary.¹⁾ The patients must be examined within 3 months after TSS.²⁴⁾ If the nadir plasma GH levels after oral glucose tolerance test are greater than 0.4 µg/L and plasma insulin-like growth factor I (IGF-I) levels are above age- and gender-adjusted normal range, the patient is not cured.²⁵⁾

If the residual tumor is visible by magnetic resonance imaging (MRI) and predicted to be resectable, the second time TSS can be considered. However, the alternative treatments should be planned, when the residual tumor is not visible by MRI.²⁶⁾

I. Dopamine receptor agonists

Dopamine receptor agonists such as bromocriptine and cabergoline have been tried to reduce plasma GH levels in patients with acromegaly. The dose and administration schedule are the same as in patients with prolactinoma. Higher dose is sometimes necessary. However, the remission rate is not sufficient. Cabergoline, a newer D2 receptor agonist, has better efficacy and less side effects than bromocriptine. It is efficient in about 40% of patient, especially in patients with mild disease activity or concomitant prolactin production.²⁷⁾ It has been reported that patients with Parkinson's disease receiving high dose of cabergoline have risks of cardiac valve disease, as mentioned earlier. The dose of cabergoline in acromegalic patients is much lower than that in Parkinson's disease.¹⁷⁾ Further studies are necessary to determine the risk of cardialvulopathy in those patients because acromegaly itself may cause the valve disease. However, dopamine agonists may be still useful in some selected patients.

II. Somatostatin analogues

Type 2 and 5 somatostatin receptors are expressed in GH-producing pituitary adenomas.²⁸⁾ Somatostatin analogues bind to them and decrease GH secretion as well as inhibit the proliferation of the adenoma

cells.²⁹⁾ The most commonly used somatostatin analogues are octreotide and lanreotide. Usually the indication of somatostatin analogues for acromegaly includes the sustained increase in plasma GH levels following initial surgery.²⁶⁾ In some patients with macroadenoma, somatostatin analogues are used as a precedent treatment.³⁰⁾ The preceding treatment with somatostatin analogue will decrease plasma GH levels and reduce the tumor size, resulting in control of complications and better remission rate of pituitary surgery.³⁰⁾ In patients with giant pituitary adenomas, it may be very difficult to achieve the remission by surgery alone.³¹⁾ Therefore, somatostatin analogues can be the first-line treatment in patients who are not predicted to be curable. In general, long-acting somatostatin analogues are administered at a low dose and adjusted to normalize plasma IGF-I levels. However, 40–50% of patients show the resistance to somatostatin analogues.³²⁾ A study of Japanese patients also showed the same results.³³⁾ In those patients, the alternative or additional therapies may be required. Common but transient side effects include nausea, white stool, abdominal discomfort, and diarrhea. In up to 20% of patients, somatostatin analogues cause cholelithiasis.¹⁾ In several reports, the preceding treatment with somatostatin analogues may act as radioprotective agents.^{34,35)} However, it is still controversial.^{36,37)}

III. GH receptor antagonist

A selective GH receptor antagonist, pegvisomant, has been developed in recent years.³⁸⁾ Pegvisomant is a recombinant GH antagonist and binds to the site one of GH receptors with high affinity and interferes the binding of native GH, resulting in inactivation of its action.³⁹⁾

In a phase III study, a very high remission rate was reported.⁴⁰⁾ Pegvisomant is started with a loading dose of 40 mg and administered subcutaneously at a daily dose of 10 mg. The dose should be adjusted to normalize plasma IGF-I levels. The monitor of plasma GH levels is not useful, because most of GH assays cross-react with pegvisomant. In addition, it must be very careful to monitor plasma IGF-I levels, because plasma IGF-I may be incorrectly low in patients with severe diabetes mellitus or malnutrition.⁴¹⁾

Pegvisomant may be more beneficial than somatostatin analogues in acromegalic patients with severe diabetes because GH antagonist has no effects on insulin secretion in contrast to somatostatin analogues.⁴²⁾ Recent results have suggested that the remission rate by pegvisomant is practically about 60%.⁴³⁾ Pegvisomant cannot decrease the size of pituitary tumor. Therefore, the first-line treatment

with GH antagonist will not be recommended at least in patients with macroadenoma. In patients who do not show good response to pegvisomant, the combination therapy with other medication such as somatostatin analogues or dopamine agonists may be beneficial.⁴⁴⁾

Pegvisomant is expensive and life-long treatment to maintain plasma IGF-I levels within age- and gender-adjusted normal range. Lipohypertrophy at the injection sites may be observed frequently.⁴⁵⁾ Theoretically, pegvisomant binds to peripheral GH receptors and leads to the decline of plasma IGF-I levels. It is difficult to deny that a decrease of plasma IGF-I level may influence pituitary adenoma through positive feedback. Therefore, the serial MRI must be performed to monitor the tumor size. It has been reported that liver damage is sometimes recognized.⁴⁶⁾

IV. In the future

Pasireotide (SOM230), a new somatostatin analogue, has high affinity to type 5 somatostatin receptors. It has been reported that in octreotide-resistant patients, the expression of type 2 somatostatin receptors is weak as compared to type 5 somatostatin receptors. Therefore, clinical trials with pasireotide are in progress.⁴⁷⁾ Interestingly, new chimeric compounds binding both dopamine and somatostatin receptors have been developed.⁴⁸⁾ These can be options for the medical treatment in the future.

Cushing's Disease

Cushing's disease is caused by the sustained hypercortisolism due to excessive secretion of adrenocorticotropin (ACTH) from a corticotroph adenoma. Its prevalence is 0.7–2.4 cases/million/year.⁴⁹⁾ Cushing's disease is still lethal disorder, unless it is diagnosed and treated appropriately. The cardiovascular mortality is about 50% in 5 years, if untreated.⁵⁰⁾ The first-line treatment is the removal of ACTH-producing pituitary adenoma by TSS.⁵¹⁾ About 65–90% of patients with pituitary microadenoma achieve remission after initial TSS.⁵¹⁾ If the residual tumor is visible by MRI, the second surgery may be considerable. The patients in whom the surgery is not successful require the alternative therapies, such as medical and/or radiation treatments. Two kinds of strategies may be applied to improve the hypercortisolism. One is the direct inhibition of ACTH secretion from pituitary adenoma and the other is the blockade of steroid synthesis in adrenal glands with steroid enzyme inhibitors. The former is theoretical but there have been few methods with high remission rate to inhibit ACTH

secretion. The latter is indisputable and sometimes rapid. When the patient shows severe hypercortisolism before surgery, it must be managed with steroid enzyme inhibitor.

I. Pituitary-directed medical treatment

As mentioned before, the first-line treatment of Cushing's disease is surgery. When surgery cannot achieve the remission, which usually means that plasma cortisol is undetectable after surgery, the pituitary-directed medication such as dopamine agonists or somatostatin analogues can be used. Each treatment should be titrated to achieve the normalization of urinary-free cortisol.

II. Dopamine agonists

Cabergoline, a specific D2 receptor agonist, has been tried to control plasma cortisol in patients with Cushing's disease. Although, in more than 50% of patients, plasma cortisol levels are initially decreased in response to cabergoline treatment, plasma cortisol levels elevate again in some of patients who show the response to cabergoline.⁵²⁾ The dose of dopamine agonist should be practically adjusted to control the urinary free cortisol excretion within normal range. Cabergoline at 0.5–4 mg/week may be required.⁵²⁾

III. Somatostatin analogue

ACTH-producing pituitary adenomas express type 2 and 5 somatostatin receptors. Recent studies reported that type 5 somatostatin receptors are more dominant than type 2 in patients with Cushing's disease in contrast to acromegaly.⁵³⁾ Somatostatin analogues having high affinity to type 2 receptors, such as octreotide, have been tried. However, the results have not been satisfactory.⁵⁴⁾ If the patients do not show any sufficient response to pituitary-directed medication, it may be recommended to switch to adrenal-directed therapy as soon as possible.

Adrenal Enzyme Inhibitors

In Japan, metyrapone, trilostane, and mitotane are available as adrenal enzyme inhibitors.⁵⁵⁾ Ketoconazole and etomidate, which are widely used as medication for Cushing's disease in the world,⁵⁶⁾ are not available in Japan. At the present time, metyrapone is the most indisputable and instantaneous. Trilostane is not recommended, when patients is emergent due to severe hypercortisolism. It takes several weeks to show the efficacy, and the effect is weak. Mitotane is an adrenolytic agent and may induce an irreversible change in adrenal glands. Also mitotane usually requires several weeks to show the effect.

I. Metyrapone

Metyrapone, an 11β -hydroxylase inhibitor, is very useful to reduce plasma cortisol levels.⁵⁶⁾ There are at least two different strategies for metyrapone administration. One is that metyrapone is started with low dose and adjusted in accordance with plasma cortisol levels. This needs couple of weeks to produce satisfactory control of plasma cortisol. The other is that the sufficient dose of metyrapone, which can strongly block the cortisol production, is administered and simultaneously given hydrocortisone as a physiological replacement. The latter usually achieve an immediate control of Cushing's syndrome and can be recommended in patients who should be quickly managed severe hypercortisolemia before surgery. For this purpose, metyrapone at 500–1000 mg is administered three times a day and hydrocortisone is replaced as in patients with hypocorticism.

II. Mitotane

Mitotane is usually used in patients with adrenocortical cancer. Mitotane therapy is called medical adrenalectomy because of its strong adrenolytic action. This leads the irreversible change in adrenocortical cells. Mitotane may be used as a substitution for bilateral adrenalectomy, if the hypercortisolemia is uncontrollable.⁵⁷⁾

In the Future

A new long-acting somatostatin analogue having high affinity to type 5 receptors, pasireotide, has been examined in patients with Cushing's disease. A phase III study reported significant results to reduce urinary-free cortisol excretion and to manage clinical symptoms.⁵⁸⁾ Although this compound deteriorates blood glucose level through inhibition of insulin secretion, it will be useful in treatment of the patients with type 2 somatostatin receptor agonists-resistant Cushing's disease. The exacerbation of the glucose tolerance may have to be treated with insulin. LCI699, a potent and long-acting 11β -hydroxylase inhibitor, has been newly developed and is more potent than metyrapone.⁵⁹⁾ This will be very beneficial for the patients with any type of Cushing's syndrome including adrenal Cushing's syndrome and ectopic ACTH syndrome.

Other Functioning Pituitary Adenoma

Thyroid stimulating hormone (TSH)-producing pituitary adenoma is very rare and presents the syndrome of inappropriate secretion of TSH. When TSS is not successful in these patients, somatostatin analogues may be effective to control hyperthyroidism.^{60,61)} Most

of the gonadotropin-producing pituitary adenomas are detected as non-functioning pituitary adenomas. In these patients, the medical management for controlling hypersecretion of gonadotropin is not required.

In patients with functioning pituitary adenoma, various medical treatments have been applicable to control the hypersecretion of pituitary hormones. Since the molecular mechanisms to regulate the pituitary hormones have been studied, new strategies and tools to manage the disease become available. However, it is true that there are still many patients who cannot achieve the remission. Therefore, further investigations are necessary.

Conflicts of Interest Disclosure

The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. The author has registered self-reported COI disclosure statement forms.

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