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Update in the medical therapy of Cushing's disease

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Abstract

Purpose of review—Recently developed agents treat Cushing's disease by inhibiting adrenocorticotropic hormone (ACTH) secretion from corticotrope tumors or antagonizing cortisol action.

Recent findings—The dopamine agonist cabergoline and the somatostatin agonist pasireotide target ACTH secretion. Each has low rates of normalization of urine-free cortisol, about 40% at doses of 1–7 mg weekly and 20% at doses of 600 or 900 μg twice daily, respectively. Cabergoline, an oral agent, has a relatively benign side-effect profile, primarily asthenia. Small trials suggest that combination therapy with ketoconazole increases effectiveness. Pasireotide, a parenteral agent, is associated with types and rates of adverse events similar to those seen with other somatostatin agonists (diarrhea, nausea, cholelithiasis), except for glucose intolerance, which occurs more frequently (~ 75%). It may be most effective when urine-free cortisol is less than two-fold normal. A few case reports suggest that pasireotide or cabergoline may control tumor size and ACTH secretion from macroadenomas. Retinoic acid must be evaluated further. The glucocorticoid antagonist mifepristone ameliorates glucose intolerance but may not normalize other Cushingoid features.

Summary—These novel approaches provide options for treatment of patients in whom surgery has failed or is not possible, and those who decline adrenalectomy or radiation therapy.

Keywords

cabergoline; Cushing's disease; mifepristone; pasireotide

INTRODUCTION

Cushing's disease, caused by a corticotropin [adrenocorticotropic hormone (ACTH)]-secreting corticotrope tumor, is best treated by surgical resection. However, the overall remission rate is 65–90%, with a recurrence rate as high as 36% [1]. Also, some patients have a clearly unresectable tumor (e.g. an invasive macroadenoma); surgery may be

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Conflicts of interest
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considered too risky (for example, an elderly person with co-morbidities) or the patient may refuse surgery. As a result, there is a need for other treatments. These alternative treatments include conventional radiation or radiosurgery, bilateral adrenalectomy and drugs. Until recently, chronic medical therapy was confined to steroidogenesis inhibitors [ketoconazole, mitotane (also adrenolytic) and metyrapone]. Their use has been reviewed recently [1] and will not be considered further except as combination therapy with newer agents. This review will highlight recent advances in the medical treatment of Cushing's disease, with agents that either inhibit ACTH secretion or antagonize glucocorticoid action.

AGENTS THAT TARGET THE CORTICOTROPE

Corticotrope tumors contain receptors and transcription factors that interact with dopamine, somatostatin, retinoic acid, and their analogues. As a result, cabergoline, pasireotide and retinoic acid hold promise as medical treatments of Cushing's disease.

CABERGOLINE

Dopamine interaction with the D2 receptor generally has an inhibitory effect. The D2 receptor is present in about 75% of corticotrope tumors [2], suggesting that dopamine agonists such as bromocriptine or cabergoline might successfully treat Cushing's disease. Trials of cabergoline built on this concept and previous reports of short-term and occasional long-term responses to bromocriptine.

A 2009 report described the ability of cabergoline to normalize UFC excretion during short-term (3 month) and long-term (12–24 months) continuation treatment of patients with persistent disease after transsphenoidal surgery [3]. If UFC remained abnormal, the initial dose, 0.5 mg twice weekly, was increased by 1-mg increments every month to a maximal dose of 7 mg/week. After 3-month treatment, seven of 20 patients had normal UFC, whereas eight patients had smaller reductions and five did not respond at all (and did not continue treatment). At 6–12 months, six of the partial responders had normal UFC. At 12 months, 10 subjects had normal UFC, and at 24 months, eight of these were controlled (two having discontinued the drug because of severe asthenia and hypotension).

Thus, overall, eight of 20 patients showed long-term normalization of UFC at a mean dose of 3.5 mg/week. Weight was not greatly changed but hypertension resolved and diabetes improved or resolved. Four patients showed tumor shrinkage. Side-effects included severe asthenia ($n = 2$), transient 'moderate' asthenia ($n = 4$) and transient dizziness with nausea ($n = 1$).

A subsequent retrospective study examined responses of 27 patients with persistent or recurrent hypercortisolism after transsphenoidal surgery, and three who received cabergoline as first-line therapy. The initial dose was 0.5–1 mg/week; this was increased every 1 or 2 months by 0.5–1 mg until UFC normalized. Fifteen of the 30 patients had a complete ($n = 11$) or partial (n = 4) response after 3–6 months. Nine patients maintained normal UFC after long-term treatment of 12–60 months at a mean weekly dose of 2.1 mg. The others escaped treatment. Unfortunately, no feature predicted the response, including tumor size, baseline

ACTH, or UFC. Three patients initially experienced transient dizziness and nausea that did not provoke drug discontinuation [4].

A case report of a woman with a macroadenoma, cavernous sinus invasion and right temporal quadrantanopsia demonstrated tumor regression of 50% and normalization of UFC over 5 years on a weekly cabergoline dose of 1.5 mg. The patient then showed clinical and biochemical recurrence of Cushing's syndrome but subsequently responded after a dose increase to 6 mg weekly [5▪].

Two studies evaluated the combination of cabergoline and ketoconazole treatment after initial treatment with a single agent. In the first, three of 12 patients with persistent hypercortisolism after transsphenoidal surgery normalized UFC after 6 months of cabergoline treatment (2–3 mg weekly). Six of the remaining 9 partial responders normalized UFC after the addition of ketoconazole (200–400 mg/d) [6].

In the second study, cabergoline (n = 6, dose up to 3 mg weekly) or ketoconazole (n = 8, daily dose of 200–600 mg) was the first agent for 4–6 months [7▪]. These patients had persistent or recurrent disease or drugs were used as the first agents. Thirteen patients had normalization of UFC with clinical improvement. However, the authors note that late night salivary cortisol levels remained abnormal in 10 patients and caution that this reflects subtle hypercortisolism that may be detrimental.

PASIREOTIDE

Pasireotide is a somatostatin analogue that preferentially binds to the somatostatin type 5 receptor, which is expressed in corticotrope tumors. Somatostatin binding to pituitary cells decreases hormone secretion and proliferation, suggesting that it might be an effective way to decrease ACTH secretion [8].

Pasireotide inhibits in-vitro basal and CRH-stimulated ACTH release from human ACTH-secreting pituitary adenomas and AtT-20 murine corticotrope tumor cells. In AtT-20 cells, dexamethasone pretreatment did not alter this response [9].

The effect of 6-month treatment with pasireotide (600 or 900 μg sc bid) on UFC and a number of secondary endpoints was studied in 162 patients with Cushing's disease who had recurrent or persistent disease after transsphenoidal surgery or who were not surgical candidates [10▪▪]. Each dose was increased by 300 μg at 3 months in patients with abnormal UFC. Twenty patients discontinued treatment by 6 months because of adverse events, 19 dropped out because of lack of efficacy and an additional 14 self-discontinued or represented a protocol violation.

At 6 months, 12 of 82 (15%) in the 600-μg group and 21 of 80 (26%) in the 900-μg group had normal UFC without a prior dose increase. Including those with a prior dose increase, 13 of 82 (16%) in the 600-μg group and 23 of 80 (29%) in the 900-μg group responded. Nonresponders could be identified as early as 2 months, as 90% of those nonresponders did not normalize at later time points.

At the end of the 12-month extension study, 11 of 82 (13%) in the 600-μg group and 20 of 80 (25%) in the 900-μg group continued to show a response. Patients most likely to respond were those with the lowest initial UFC (1.5–2-fold the upper limit of normal) who received 900 μg injections; seven of 14 patients in this group showed a response, compared with one of 22 at this dose whose baseline UFC was more than five-fold normal. There was a decrease in tumor volume of −9.1% in the 600-μg dose and −43.8% in the 900-μg dose group.

The rate and type of adverse events were similar to those seen with other somatostatin analogues (diarrhea, nausea, cholelithiasis), except for glucose intolerance, which occurred more frequently [10▪▪,11▪,12▪]. Overall, 118 of 162 (73%) patients had a hyperglycemia-related adverse event. Ten of 162 (6%) discontinued treatment because of this, and a new antidiabetic medication was started in 74 of 162 (46%). The European Medicines Agency (EMA) recommends assessment of HbA1c before treatment with pasireotide and notes that hyperglycemic events were more common in patients with diabetes or glucose intolerance, and in those receiving a dose of 900 μg. It recommends blood glucose monitoring weekly for 2–3 months, and then interval HgbA1c measurement [12▪].

Increased hepatic aminotransferase levels were observed in 16%; 5% had values greater than three times the upper limit of normal [11▪]. The EMA recommends monitoring liver function tests before and 1, 2, 4, 8 and 12 weeks during treatment, with subsequent testing based on clinical judgment [12▪]. Eight percent of patients developed symptoms of adrenal insufficiency.

Pasireotide is the first agent approved by the EMA and Food and Drug administration (FDA) (as Signifor) for the treatment of Cushing's disease. However, the FDA is requiring three postmarketing studies: a clinical trial to assess hyperglycemia management; a long-term prospective observational cohort study (registry) of patients with Cushing's disease treated with Signifor; and focused safety monitoring for reports of serious hyperglycemia, acute liver injury, and adrenal insufficiency [11▪].

The use of long acting release pasireotide 60 mg every 8 days in a woman with Nelson's syndrome was associated with improvement in hyperpigmentation, decreased ACTH and decreased suprasellar tumor extension [13▪]. The patient developed hyperglycemia that required medical management.

COMBINATION THERAPY

One study evaluated the sequential addition of ketoconazole and/or cabergoline to pasireotide therapy when patients did not respond to initial and/or subsequent treatment [14]. In this study, 17 patients initially received pasireotide 100 μg three times daily, with an increase to 250 μg/dose if the UFC did not normalize in 2 weeks. Cabergoline (0.5–.5 mg every other day) was added if there was no response at 1 month, and ketoconazole (200 mg three times daily) was added to nonresponders on day 60. Normal UFC was achieved in five patients with pasireotide, four with pasireotide and cabergoline, and six taking all three medications, for an overall response rate of 88%.

Both pasireotide and ketoconazole can prolong the Q-T interval [12▪] and should be used with caution in patients who are at risk for development of this abnormality. Additionally, ketoconazole inhibits p-glycoprotein, and pasireotide is a p-glycoprotein substrate, which might possibly increase pasireotide concentrations. Their combined effect on the QT interval was not evaluated in this study.

RETINOIC ACID

The potential use of retinoic acid for the treatment of Cushing's disease was suggested by in-vitro studies showing that it reduced ACTH secretion by human corticotrope tumor cells and decreased proliferation, leading eventually to cell death [15]. Retinoic acid also reduced AtT-20 tumor growth and ACTH secretion in nude mice [15] and reduced tumor size and ACTH and cortisol secretion in a dog model of spontaneous Cushing's disease [16].

A recent prospective study evaluated the effects of retinoic acid, up to 80 mg daily, on UFC, plasma ACTH and clinical and biochemical features, in seven patients with Cushing's disease [17▪]. Three patients had sustained normalization of UFC. Plasma ACTH decreased initially but returned to basal levels. Adverse events included arthralgias (n = 3), dry eye and mouth (n = 3), diarrhea (n = 2) and headache (n = 1), as previously associated with this agent.

ANTIGLUCOCORTICOID TREATMENT OF CUSHING'S DISEASE

Mifepristone is a steroid that antagonizes the action of progesterone and cortisol. The latter property accounts for its ability to improve the clinical and biochemical features of Cushing's syndrome. However, because of its mechanism of action, cortisol and ACTH levels cannot be used to assess response [18] Fleseriu *et al.* [19▪▪] evaluated the response to mifepristone in an open-label study. Thirty-four of 50 enrolees completed the 24-week study. Each had a confirmed diagnosis of Cushing's syndrome and either diabetes/glucose intolerance or hypertension. The primary endpoint was a 25% or more decrease in the area under the curve of an oral glucose tolerance test (OGTT) or a decrease in diastolic blood pressure of at least 5 mmHg. The starting daily dose of 300 mg was increased by 300 mg at weeks 2, 6 and 10 if there was no clinical improvement. A calculated composite clinical response gave points to mood, weight loss and improvement in other features of Cushing's syndrome.

After 24 weeks of treatment, 15 of 25 patients with diabetes met the OGTT endpoint, and had a decrease of fasting blood glucose from 149 to 105 mg/dl. Eight of 21 patents with hypertension met the diastolic blood pressure endpoint. Of 40 patients with both diabetes and hypertension, 11 had a decrease in antihypertensive medications and 21 had a decrease in diastolic blood pressure or medications. Forty of 46 patients decreased their clinical score by at least one point, but normalization of this score was not addressed.

The most common side-effects were hypokalemia (34%) and symptoms consistent with adrenal insufficiency [nausea (48%), fatigue (48%), headache (44%) and arthralgia (30%)]. Eighty-eight percent of patients had at least one adverse event and seven patients discontinued medication because of an adverse event.

The FDA approved the use of mifepristone (as Korlym), 300 g daily, to control hyperglycemia secondary to hypercortisolism in adults with endogenous Cushing's syndrome who have failed surgery or are not candidates for surgery. Because the extent of clinical improvement was not described, the role of mifepristone apart from treatment of hyperglycemia is not clear. Mifepristone has not been tested in combination with any of these other newer agents. However, it induces CYP3A4 and inhibits p-glycoprotein function, so that these effects should be considered if combined therapy is evaluated [20].

CONCLUSIONS

Mifepristone is FDA-approved for treatment of diabetes in Cushing's syndrome. Pasireotide is approved for the treatment of Cushing's syndrome. Cabergo-line treatment of Cushing's disease represents an off-label use.

There are limited data on the use of pasireotide, cabergoline, retinoic acid or mifepristone mono-therapy for the treatment of Cushing's disease (Table 1) [3,4,6,7▪,10▪,11▪,12▪,14]. Cabergoline and pasireotide have low rates of UFC normalization and data are too few to judge retinoic acid. Mifepristone has low rates of clinical normalization. The two small studies that addressed combination therapy (cabergoline and ketoconazole with/without pasireotide) suggest that it may more effectively normalize UFC. Clearly additional data are needed to help evaluate the role of these agents.

Normalization of clinical features and reduction in morbidity and mortality remain the goals of all treatments of Cushing's syndrome [21]. The studies of agents that affect the corticotrope all had UFC primary endpoints and the study with mifepristone had limited biochemical endpoints that would allow for a 'response' without normalization of OGTT or clinical features. Longer-term studies are needed to confirm the preliminary findings, to better assess side-effect profile and to judge whether patients normalize the features of Cushing's syndrome, and experience less morbidity and mortality. Until such studies are done, these agents will likely be used as second-line therapy for patients who are not eligible for transsphenoidal surgery or adrenalectomy, or in whom other medical therapy has failed.

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KEY POINTS

- Cabergoline is an oral agent that normalizes urine-free cortisol (UFC) in about 40% of patients with Cushing's disease.
- Pasireotide, a parenteral agent with an overall response rate of about 20%, is associated with a high rate of hyperglycemia, and may be best suited for patients with basal UFC less than two-fold normal who are not diabetic.
- Mifepristone is approved for the treatment of hyperglycemia in Cushing's syndrome; its ability to reverse other Cushingoid features is not clear.
- There are insufficient data to recommend the routine use of combination therapy or monotherapy with retinoic acid.

Table 1

Medical treatments of Cushing's disease that target the corticotrope: Cabergoline (C), and Pasireotide (P), with or without the steroidogenesis inhibitor Ketoconazole (K)

Agent (ref)	Dose	Normal UFC, n/total (%)	Decrease in tumor size	Adverse events
C [3]	1–7 mg/week	8 of 20 (40%)	+ 4 of 20 pts	Asthenia, dizziness, nausea
C [4]	1–7 mg/week	9 of 27 (33%)	ND	
P, C, K, [14]	P 100–250 mg TID	5 of 17	ND	Hyperglycemia, decreased IGF-1
	+ C 0.5–1.5 QOD	4 of 12		
	+ K 200 TID sequentially, if no response	6 of 8 (overall 88%)		
C + K [6]	C 2–3 mg/week	3 of 12	ND	C: dizziness and/or nausea (n = 3)
	+ K 200–400 mg/d	6 of 9 (overall 75%)		K: mild increase LFT
C + K [7▪]	C to 3 mg/week	13/14 (10 had abnormal LNSC)	ND	K: one case increased LFT, one case skin rash
	+ K 200–600 mg/d			
P [10▪▪,11▪,12▪]	600 mg BID	11/82 (13%)	39.1%	diarrhea, nausea, cholelithiasis, hyperglycemia
	900 mg BID	20/80 (25%)	343.8%	

C, cabergoline; K, ketoconazole; LFT, liver function tests; LNSC, late night salivary cortisol levels; ND, not done; P, pasireotide; IGF-1, Insulin-like growth factor 1.