Medical Management of Persistent and Recurrent Cushing Disease

Maria Fleseriu, MD[a,b,*]

KEYWORDS

• Cushing disease • Failed transphenoidal surgery • Recurrent Cushing disease
• Somatostatin receptor ligands • Pasireotide • Glucocorticoid receptor antagonist • Mifepristone
• Adrenal steroidogenesis inhibitors

KEY POINTS

- The prevalence of Cushing disease seems to be higher than previously thought.
- Morbidity and mortality are significantly increased in untreated hypercortisolemia.
- Transphenoidal surgery, in the hands of experienced neurosurgeons, is currently considered the first-line treatment of choice.
- A significant number of patients with Cushing disease could require additional medical treatment at some point in their disease course (either after failed pituitary surgery or after disease recurrence, which can be seen as late as 20 years after initial treatment).
- New therapeutic agents, such as pasireotide (a multiligand somatostatin receptor ligand that targets the corticotroph adenoma itself) and mifepristone (a glucocorticoid receptor antagonist), have recently been approved in Europe (pasireotide for treatment of Cushing disease) and the United States (mifepristone for treatment of hyperglycemia associated with Cushing syndrome).
- Individualized, multidisciplinary management to normalize devastating disease effects of hypercortisolemia is required.

INTRODUCTION

Cushing syndrome (CS) is a severe clinical state produced by prolonged and inappropriate exposure to endogenous or exogenous cortisol. The exogenous cause is usually identifiable; in contrast, diagnosis of excessive pituitary adrenocorticotropic hormone (ACTH) secretion sometimes is more complicated, especially in the early disease phase. The true incidence and prevalence of CS is difficult to estimate because of the rarity of the disorder, its insidious onset. Diagnosis is also complicated by nonspecificity and high prevalence of clinical symptoms in the general population. Furthermore, the diagnostic work-up of suspected CS requires a variety of combined biochemical tests, which often have inadequate sensitivity and specificity. Early data suggested a prevalence of 0.7 to 2.4 per million.[1] However, several recent studies have suggested

Disclosure: MF serves as investigator on research grants to OHSU from Corcept Therapeutics, Inc and Novartis. She also serves as an ad hoc consultant to Novartis.

[a] Department of Medicine, Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road (BTE 472), Portland, OR 97239, USA; [b] Department of Neurological Surgery, Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road (BTE 472), Portland, OR 97239, USA
* Northwest Pituitary Center, Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road (BTE 472), Portland, OR 97239.
E-mail address: fleseriu@ohsu.edu

Neurosurg Clin N Am 23 (2012) 653–668
http://dx.doi.org/10.1016/j.nec.2012.06.012
1042-3680/12/$ – see front matter

a much higher prevalence for Cushing disease (CD) and CS.[2,3]

Moreover, epidemiologic studies in Belgium and England have revealed that the prevalence of clinically relevant pituitary tumors is 3.5- to 5-fold higher than previously estimated with an incidence rate of approximately 76 to 100 per million.[4,5] ACTH-secreting adenomas represent approximately 10% to 15% of all pituitary tumors; therefore, CD rates could be substantially higher than previously estimated.[1,6] Additionally, screening for CS in certain patient populations has revealed a prevalence of up to 3% to 11% in patients with diabetes, obesity, and osteoporosis.[7–9]

The most common etiology (70%–80%) of CS is CD, caused by an ACTH-secreting pituitary adenoma. Women are affected more than men (5:1), with peak incidence at 25 to 40 years of age.

MORBIDITY AND MORTALITY

CS is associated with increased cardiovascular morbidity and mortality. Chronic hypercortisolemia is responsible for a higher incidence of hypertension, glucose intolerance, diabetes mellitus, central obesity, hyperlipidemia, and hypercoagulability.[10] Recent evidence also suggests that increased cardiovascular risk may persist even after long-term CS remission.[11–16]

In a 2011 study, Clayton and colleagues[17] calculated standardized mortality ratio for a group of their own patients; persistent CD (adjusted for age and gender) versus CD in remission was 10.7 versus 3.3, respectively. Standardized mortality ratio data for six other studies they reviewed were 5.5 versus 1.2 in persistent CD versus CD in remission. Hypertension and diabetes mellitus were risk factors of worse outcome, as well as disease persistence and older age at diagnosis.[17] In another review of three larger studies,[18] patients with persistent CD experienced a marked increase in mortality rate compared with those experiencing initial cure (mortality rate of 3.25).

These results suggest that in patients with persistent CD early and aggressive intervention to prevent excessive mortality is required.

TREATMENT

Successful Management

For as long as CS has been described, the syndrome has presented a challenge to physicians and patients alike. Treatment goals for CD include the reversal of clinical features, the normalization of cortisol levels with minimal morbidity while preserving pituitary function, and long-term disease control without recurrence.[19] In a small number of patients with macroadenomas, removal of the tumor mass represents an additional treatment goal.

First-line therapy in most cases is transphenoidal surgery (TSS), but even in the hands of the most experienced neurosurgeon, cure rates can range from 65% to 90% for microadenomas (with even lower percentage cure rates for macroadenomas). Unfortunately, cure rates have been noted to drop further with longer follow-up.[20,21] The outcomes of TSS for CD have recently been reviewed in detail.[22,23] An accurate measurement of real outcome data is hampered by different definitions of cure or interval assessments in various studies.[24] For example, postoperative patients could be considered as in complete remission or cured, remission with relapse, or not cured with persistent hypercortisolism.[25,26]

Furthermore, even for patients who are “cured,” the risk of relapse over time is relatively high with long-term follow-up.[14,27,28] Thus, a diagnosis of remission rather than “cured” is preferable. Unfortunately, there is no ideal predictor of what could be considered permanent remission. Postoperative adrenal insufficiency has been shown to be less reliable than initially thought.[6] Conversely, a normal or slightly high postoperative cortisol level is not an absolute indicator of not being in remission. A recent multicenter study showed that 5.6% of patients, who had an initial normal or slightly high urine free cortisol (UFC) level, developed a delayed and persistent cortisol decrease after an average of 1 month postoperatively.[14] An immediate postoperative cortisol level, especially if high, could be important for a decision regarding early repeat surgery.[6,14,29]

If first-line surgery is unsuccessful, the next treatment step is presently somewhat dependent on the patient or treatment center preference. In all cases of persistent or recurrent CD, successful treatment requires close collaboration between endocrinologists, neurosurgeons, radiation oncologists, and general surgeons (**Fig. 1**).

Screening tests and localization tests are fraught with false-positives and negative results. If a patient fails surgery (unless pathology is positive for ACTH-secreting adenoma), a diagnosis reconfirmation is recommended[6] before any further treatment decision can be made.

Medical Treatment

Recently, medical treatment has played a more important role in controlling cortisol excess and its devastating physiologic effects.[21,30] Results of two large phase III prospective trials conducted over the last few years have been published that

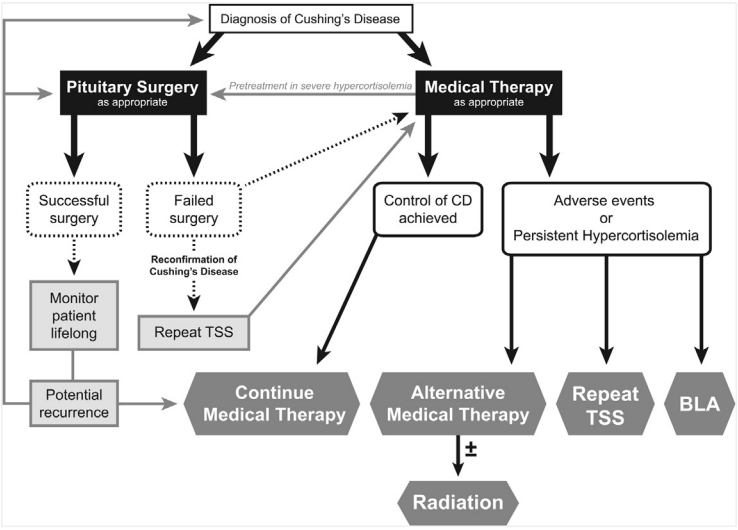

Fig. 1. Treatment of Cushing disease. BLA, bilateral adrenalectomy; CD, Cushing disease; TSS, transphenoidal surgery.

could have an impact on treatment perspective (reviewed in detail next).

Pasireotide (Signifor) has been approved in Europe for treatment of CD and mifepristone (Korlym) has been approved by the US Food and Drug Administration for hyperglycemia associated with endogenous CS. Currently, uses of medication include preparation for surgery (to control the metabolic effects of hypercortisolemia) or as adjunctive treatment after surgery.[31] Medications are also of use in patients who are unwilling or have contraindications to surgery and are awaiting effects of radiation.[6] Mirroring the treatment approach to acromegaly (to a different extent), primary medical therapy (that is replacing surgery) has also been used in patients with CD in clinical practice or research clinical trials.[32–36] It is essential that patients be counseled about the need for lifelong medical therapy in such cases because hypercortisolemia recurs on treatment discontinuation.

A brief review of treatment options after failed first-line TSS for CD is detailed next. The remainder of the discussion focuses on medical therapy.

Repeat TSS is a good option in selected cases, achieving remission in 43% to 70% of patients.[23,37,38] The risk of hypopituitarism is higher after repeat surgery compared with the first TSS, and ranges from 41% to 50%.[39,40]

Radiation (conventional and stereotactic) plays a role in patients with large tumors that invade the cavernous sinus or in patients who experience relapse after an initial cure with no observed tumor on magnetic resonance imaging.[6] Radiation therapy outcome studies in patients with CD have been summarized by Tritos and colleagues.[23] Up to 86% of patients experienced hypercortisolemia remission and tumor growth was controlled in most cases. Unfortunately, similar to the surgical series, different criteria and assessment timelines were used to measure remission. Effects of radiation are usually observed at 2 to 5 years and patients require interim medical treatment to control hypercortisolemia.[25] Besides the general risks related to radiation, hypopituitarism was observed in almost half of the patients at 5 years.[41]

Bilateral adrenalectomy (BLA), the first reported treatment for CS, offers quick control of hypercortisolemia. Currently, laparoscopic BLA has a role in patients who have failed all other options, or in women who wish to become pregnant.[42] Despite being a definite treatment for CS, patients experience permanent adrenal insufficiency with a need for lifelong glucocorticoid and mineralocorticoid replacement. In addition, corticotroph tumor progression is observed in up to 30% of cases.[43]

MEDICAL THERAPY

Mechanism of action and a summary of drugs commercially available and under clinical investigation are provided in **Table 1** and **Fig. 2**.

Modulation of ACTH Release

ACTH hypersecretion is still under hypothalamic control in CD, thus the potential therapeutic role for neuromodulatory agents. Bromocriptine, cyproheptadine, octreotide, and valproate have yielded variable efficacy and only marginal results.[44,45] Spontaneous remission of CD could explain discrepant results in small studies.

Table 1
A summary of drugs, commercially available and under clinical investigation

A	Glucocorticoid receptor blocker (act to block effects of hypercortisolemia)	Mifepristone
B	Modulate ACTH (act at the tumor level to modulate ACTH release)	Somatostatin receptor ligands: • Pasireotide–SOM 230 • Octreotide Dopamine agonists • Cabergoline • Bromocriptine Other agents tried but not uniformly effective • GABA agonists • Valproic acid • Serotonin antagonists • PPAR gamma In vitro/animal models • Alpha 1 adrenergic receptor antagonist • Retinoic acid • EGFR inhibitors
C	Inhibitors of steroidogenesis (blockage of adrenal enzymes implicated in cortisol synthesis)	• Ketoconazole • Mitotane (approved in Europe) • Etomidate • Metyrapone • Ketoconazole + Metyrapone + Etomidate • Aminoglutethimide (no longer available) • Trilostane (no longer available) In clinical trials • LCI (www.clinicaltrials.gov)
D	Combination therapy using drugs from different groups	• Pasireotide + Cabergoline + Ketoconazole

Recently, studies have shown that the dopamine D_2 receptor is expressed in 75% of corticotroph adenomas[46] and somatostatin receptor SSTR5 is predominantly expressed in cultured human corticotroph adenoma cells.[47,48] These data have renewed interest in dopamine agonists and somatostatin receptor ligands (SRLs) as potential CD therapeutic agents (see later).

Cyproheptadine is a histamine and serotonin (5-HT) antagonist previously used in patients with Nelson syndrome. It has been postulated that ACTH secretion is under a degree of serotoninergic central nervous control or that cyproheptadine has a direct inhibitory effect on corticotropin-releasing hormone (CRH) and vasopressin secretion from the hypothalamus (in vitro studies).[49]

One patient with CD was remarkably controlled for a period of 11 years,[50] but other patients have experienced disappointing results.[19,44] Doses have varied between 12 and 24 mg/d. The most commonly encountered side effects are sleepiness and weight gain, which represent the main cause for treatment discontinuation.

Valproic acid is an antiepileptic agent that inhibits γ-aminobutyric acid aminotransferase. Earlier studies showed a significant reduction in ACTH levels,[51] but chronic administration was not associated with similar results.[45] As is the case with other neuromodulatory agents, the exact mechanism of action is not well understood, but most likely acts at the hypothalamic level or on CRH secretion.

Peroxisome proliferator-activated receptor (PPAR)-γ is a member of the nuclear receptor superfamily, and functions as a transcription factor. ACTH-secreting adenomas highly express PPAR-γ.[52] Despite initial reports that PPAR-γ ligands could play a role in treating CD,[53,54] current results do not sufficiently support routine clinical use.[19,55]

Dopamine agonists: bromocriptine and cabergoline

Bromocriptine and cabergoline have shown in vitro inhibition of ACTH secretion in corticotroph tumor cells.[46] Bromocriptine is a potent dopamine receptor agonist and cortisol levels are reduced after just one dose; however, long-term cortisol

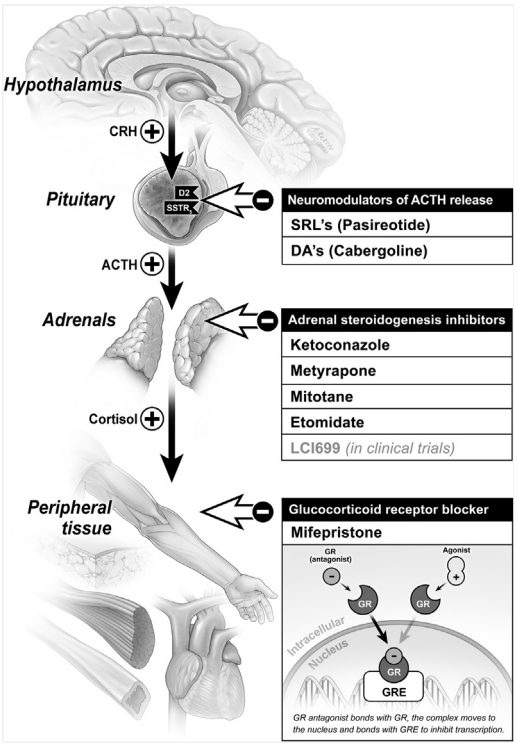

Fig. 2. Mechanism of action and targets for therapy in Cushing disease. ACTH, adrenocorticotropic hormone; DA, dopamine agonist; GR, glucocorticoid receptor; GRE, glucocorticoid response elements; SRL, somatostatin receptor ligand.

reduction results are at best 30% to 50%.[44,56] Bromocriptine effectiveness was initially reported for Nelson syndrome[57] and in CD with associated tumor shrinkage, but long-term response was limited.[58] In 12 patients with CD after BLA (no evidence of a pituitary adenoma), plasma ACTH showed a small but significant overall reduction after bromocriptine therapy.[59] Addition of cyproheptadine did not offer additional benefits.

Dopamine agonist use is associated with adverse effects, such as nasal congestion, nausea, and postural hypotension, although a gradual increase in dose could minimize these effects.

Cabergoline has recently been added to the treatment armamentarium in patients with CD who have failed surgery. It has a much longer half-life and a very high affinity and specificity for D_2 receptors. Short-term results have been encouraging in monotherapy and in combination therapy (reviewed elsewhere in this article).

As with bromocriptine, cabergoline efficacy (0.5 mg twice a week) was initially reported for Nelson syndrome.[60] In this particular case, bromocriptine treatment had failed and 12 mg/d cyproheptadine for 18 months significantly decreased ACTH levels and partially improved pigmentation, but was ultimately stopped because of adverse effects.

In multiple CD case reports, treatment with cabergoline resulted in a short-term response in up to 75%[61,62] of patients. In long-term studies cabergoline has been found to induce a complete response in selected patients (25%–40%) in studies lasting 6 to 24 months.[62,63]

Retrospectively, Godbout and colleagues[35] studied 30 patients with CD (first-line treatment for three patients) treated with cabergoline over the long term. Initial dosing was 0.5 to 1 mg/wk, which was increased up to 6 mg/wk in 80% of patients, a much higher dose than previously reported. Complete response to treatment (normal serial UFC) was initially observed in 36.6% of patients; however, after a mean of 37.7 months, just 9 (30%) of 30 patients were considered controlled (mean dose was 2.1 mg/wk) (**Fig. 3**). It was also noted that the patients with a partial initial response were not controlled at follow-up and that two patients presented an escape phenomenon at 2 and 5 years, respectively. Severity of disease was not shown to influence outcome. Cabergoline was well tolerated overall. Interestingly, despite theoretical concerns, no significant cardiac valvulopathy was seen in this study or in Pivonello's study[63]; longer-term studies are needed to elucidate the potential cardiac involvement.

Somatostatin-receptor ligands

Native somatostatin (binds to all five somatostatin receptors subtypes with high affinity) has been

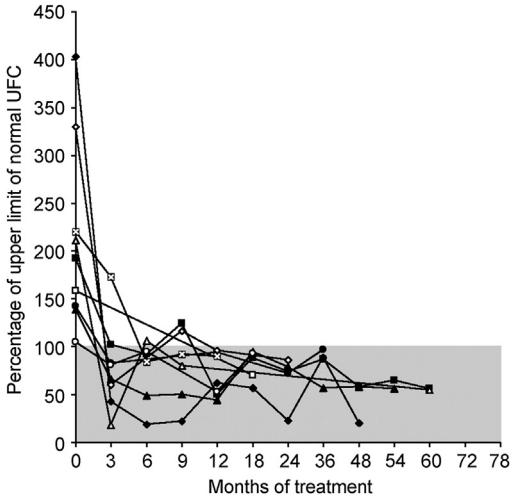

Fig. 3. Complete long-term response to cabergoline monotherapy in nine patients with Cushing disease. (*From* Godbout A, Manavela M, Danilowicz K, et al. Cabergoline monotherapy in the long-term treatment of Cushing's disease. Eur J Endocrinol 2010;163(5):709–16; with permission.)

shown to inhibit CRH-stimulated ACTH release in normal rat pituitary cells, when incubated in serum-deprived conditions or after pretreatment with a glucocorticoid-receptor blocking agent.[64]

Octreotide, an SRL that predominantly targets SSTR2 and has been extensively used with other neuroendocrine tumors, was also studied in a variety of CS cases. In vitro, octreotide-inhibited CRH stimulated ACTH secretion but in vivo did not have any effects on basal or CRH-stimulated ACTH. This discrepancy could be related to down-regulation of SSTR2 by hypercortisolemia[65] and could explain some of the positive results observed in Nelson syndrome versus CD.[66]

Predominant expression of SSTR5 mRNA in cultured human corticotroph adenoma cells[47] prompted an alternative approach using an SST5 ligand.[67]

Pasireotide (SOM 230) is a novel multireceptor-targeted SRL that has shown efficacy in patients with acromegaly and CD when administered by subcutaneous injection.[68,69] Pasireotide (**Fig. 4**) demonstrates high binding affinity for SST1, SST2, SST3, and SST5, and has a 40-fold higher affinity for SST5 than octreotide.[70]

Pasireotide has been found to exhibit enhanced potency in murine corticotroph cells as evidenced by cyclic adenosine monophosphate accumulation and calcium oscillations (important markers of ACTH secretion).[71,72] Pasireotide action seems to be determined primarily by SST5, whereas the ligand effect on SST2 is negligible. Cell proliferation and ACTH secretion were also suppressed by pasireotide in primary cultures of human corticotroph tumors.[67] In a phase II, proof-of-concept, open-label, single-arm, multicenter study, the in vivo efficacy of pasireotide was evaluated in 39 subjects with either de novo or with persistent or recurrent CD.[68] Pasireotide, 600 μg, was given subcutaneously twice daily for 15 days: mean UFC level decreased in 76% of subjects and normalized in 17%. Responders seemed to have higher pasireotide exposure than nonresponders. The authors noted a trend toward lower baseline UFC levels as predictive of a response to pasireotide with significantly greater reductions in serum cortisol in UFC responders versus nonresponders. In addition, reductions in serum cortisol and plasma ACTH were seen with significant improvement in clinical symptomatology.

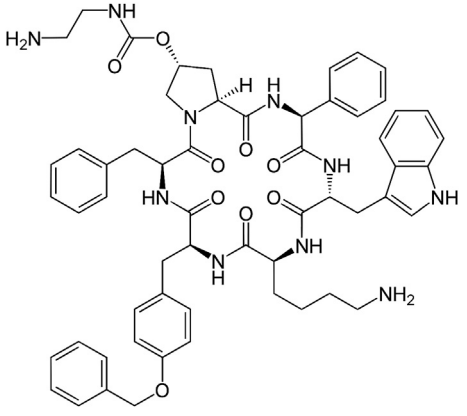

Fig. 4. Chemical structure of pasireotide.

A subsequent double-blinded phase III trial with pasireotide (600 or 900 μg twice daily) revealed UFC reduction in most patients.[34] Normalization of UFC at 6 months without the need for dose titration (primary endpoint) was achieved in 14.6% of the 600-μg group and 16.3% of the 900-μg group. If patients had a dose increase at Month 3, this percentage increased to 16% and 29%, respectively. Response rate in mild CD (UFC >1.5–2 XULN) was even higher, up to 50% in the 900-μg group (**Fig. 5**). As mean UFC decreased, clinical signs (systolic and diastolic blood pressure) and symptoms and quality of life improved. Low-density lipoprotein cholesterol and weight decreased significantly ($P<.001$). Serum and salivary cortisol and plasma ACTH were also reduced. Of utmost significance, if present, response was rapid and sustained; responders (based on UFC levels) were identified early in most cases, within 2 months of treatment. Tumor volume also decreased, by up to 43.8% (95% confidence interval, decrease range 68.4%–19.2%). Adverse effects were similar to that of other SRLs (mostly transient gastrointestinal discomfort), except for hyperglycemia; 73% of subjects had a hyperglycemia-related adverse effect and 6% discontinued the study because of such events. In these patients, close monitoring of glucose levels and prompt treatment for hyperglycemia is essential. Thirteen (8%) subjects had an adverse effect of hypocortisolism that was responsive to a dose reduction. Based on these study results, pasireotide (Signifor) has recently been recommended by the Committee for Medicinal Products for Human Use of the European Medicines Agency for approval to treat CD in Europe.[73] Clinical studies using monthly pasireotide long-acting-release in CD are ongoing (www.clinicaltrials.gov). This drug represents an important advance in treating CD with a pituitary-directed therapy that decreases ACTH, cortisol values, and corticotroph tumor volume.

Potential new receptor targets: in vitro and animal models

Retinoic acid receptors are important drug targets for cancer therapy and prevention.[74,75] Retinoic acid

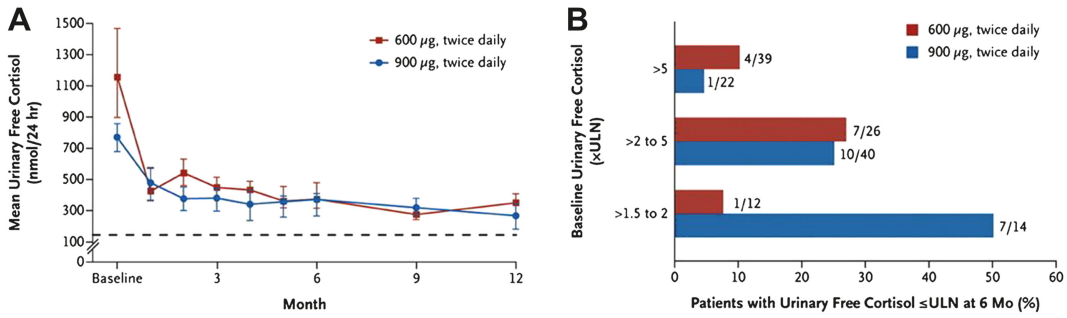

Fig. 5. Mean change in urinary free cortisol levels from baseline to Month 12 and proportion of patients with normalized levels at Month 6. ULN, upper limit of normal. (*From* Colao A, Petersenn S, Newell-Price J, et al. A 12-month phase 3 study of pasireotide in Cushing's disease. N Engl J Med 2012;366:914–24; with permission.)

has been shown in vitro and in animal studies to have a potent inhibitory effect on corticotroph tumor growth, plasma ACTH, and corticosterone secretion.[75,76] α_1-Adrenergic receptor antagonists have also been shown to decrease plasma ACTH and decrease tumor growth in murine pituitary cells.[77]

The epidermal growth factor receptor (EGFR) family has recently been studied as a therapeutic target for CD. Melmed's group[78] showed in surgically resected human and canine corticotroph cultured tumors that blocking EGFR activity with gefitinib (an EGFR tyrosine kinase inhibitor) attenuated pro-opiomelanocortin expression, inhibited corticotroph tumor cell proliferation, and induced apoptosis. In mice, gefitinib treatment decreased tumor size and corticosterone levels and reversed signs of hypercortisolemia, including elevated glucose levels and excess omental fat. These results indicate that inhibiting EGFR signaling may be a novel strategy for treating CD.[78] Efficacy in patients with CD has not yet been tested in clinical trials.

Drugs that Inhibit Steroidogenesis

These drugs decrease cortisol production by complete or partial direct inhibition of adrenal steroidogenesis: ketoconazole, mitotane, etomidate, metyrapone, trilostane, and aminoglutethimide. However, metyrapone, aminoglutethimide, and trilostane are no longer available in the United States. Combinations of these drugs may have additive or synergistic effects, achieving similar results with lower doses and less adverse effects.

Ketoconazole is an imidazole derivative that impairs steroid hormone synthesis by blocking mitochondrial P-450–dependent enzyme systems (inhibition of 17,20-lyase, adrenal 11β-hydroxylase, 17-hydroxylase and side chain cleavage).

Excluding those studies with less than five patients, there are now more than 150 patients with CD who have been treated with ketoconazole.[33,79] Remission rates vary from 30% to 90%.[33] However, some study results may have been biased by previous pituitary radiation treatment.[80]

The first large retrospective study of patients with CD treated with ketoconazole included 28 patients with CD. Twelve patients were treated for more than 6 months with good results overall; all patients had undergone pituitary irradiation.[80] Ketoconazole has also been used in three patients older than 75 years of age with good results and no adverse effects.[81]

In most of the initial studies, dose ranged from 200 to 1200 mg/d.[82] Liver toxicity was also variable and ranged from 12% to 50%.[83–86] In addition to liver problems (hepatic dyscrazia and elevated transaminases), gastrointestinal disturbances, gynecomastia, and sexual side effects were also observed. Ketoconazole is contraindicated in pregnant women.

In the largest study to date,[33] 38 patients with CD treated long-term (range, 6–72 months; mean, 23 months) with ketoconazole were reviewed, most as primary therapy (21 patients); the other 17 patients had previously undergone TSS. Ketoconazole dose was 200 to 1200 mg daily with 45% of patients considered responders based on the intention-to-treat analysis. Five patients stopped taking the drug within 1 week because of intolerance. Interestingly, 5 of 15 patients who did not have a pituitary adenoma initially had a visible tumor after 20 to 30 months of treatment. There was no adrenal insufficiency with the titration used in the study. Responders were identified early in the treatment course (all controlled patients responded within 3 months of the treatment start). Unfortunately, none of the initial biochemical parameters were good predictors of response.

An ACTH increase is expected with most adrenal steroidogenesis inhibitor drugs but there

have been initial reports that ketoconazole prevents the expected rise in ACTH secretion, thus allowing maintenance of the same dose.[26,87] Reduced negative cortisol feedback after enhanced response of ACTH to CRH administration has been postulated to play a role.[88] Other studies have not confirmed a direct effect of ketoconazole on ACTH.[89]

Ketoconazole has inhibitory effects on several cytocrome P-450 enzymes (mainly CYP3A4, CYP2C9, CYP1A2); thus, a multiple drug-drug interaction is possible. The most frequently used medications, which require dose adjustments, are most benzodiazepines; calcium channel blockers; statins (excluding pravastatin and fluvastatin); warfarin; phenytoin; and fluoxetine.[90]

Ketoconazole absorption requires an acidic environment, precluding the use of proton pump inhibitors or H_2 receptor blockers. Because of over-the-counter availability of both of these drug classes, it is important that this is discussed with patients before starting treatment (**Box 1**).

Mitotane (o'p'-DDD) is an adrenocorticolytic drug that also inhibits the same enzymes as etomidate. It is mainly used to treat adrenocortical carcinoma, but it seems to have some suppressive ACTH effects. Eighty percent of patients treated with mitotane and pituitary radiation have been reported as in remission.[91]

In a recent retrospective large cohort of 76 patients with CD treated with mitotane at a single center, 24-hour UFC normalization was observed in 48 (72%) patients, with a median follow-up of 6.7 months. Adverse events led to discontinuation in 29% of patients. A pituitary adenoma became visible during treatment in 12 patients (25%) with initial negative pituitary imaging allowing subsequent TSS. Fortunately, 29% of patients were in remission even after stopping the drug; high plasma ACTH at the time of treatment discontinuation was statistically associated with a lower recurrence probability.[32]

Box 1
Clinical practice

- Ketoconazole at a dose of 200 mg two or three times daily, and check liver function and 24-hour UFC within 1 week.
- If clinical signs of adrenal insufficiency, measure morning cortisol as soon as possible, stop drug for 1 day. Start replacement glucocorticoids if needed.
- If UFC still high, increase to 400 mg twice daily.
- If not well tolerated or no effect in 2 to 3 months, switch to a different drug.
- Consider possible combination therapy.

Data from references.[6,25,33,44]

The usual dose is approximately 4 g/d (gradually increasing the dose from 0.5–1 g daily), given with fat-containing food. Doses of 12 g daily[92] have been reported; nausea seems to be dose dependent.[44]

Mitotane increases exogenous steroid clearance[44]; therefore, the replacement dose needs to be adjusted. There are also induced changes in corticosteroid-binding globulin, potentially making plasma cortisol measurements less reliable. Adverse effects are represented by gastrointestinal symptoms, rash, confusion, gynecomastia, and hepatotoxicity.

Mitotane is completely contraindicated in women who are planning pregnancy over several years because the drug has been detected in adipose tissue long after discontinuation.[93] Sometimes mitotane spares aldosterone secretion, a potential advantage over surgical adrenalectomy.

Metyrapone (not commercially available compassionate use) inhibits 11β-hydroxylase when used in single or combination therapy[94,95] with good results overall, in up to 75% of patients.[19] Doses range from 500 to 6000 mg daily. Adverse effects are mainly hirsutism and acne in women, dizziness, gastrointestinal upset, and hypokalemia. Although contraindicated in pregnancy, it is the agent most frequently used in CS associated with pregnancy.[96] Compensatory increases in ACTH are seen, mostly at the beginning of the treatment.[95]

Trilostane, a 3β-hydroxysteroid dehydrogenase selective inhibitor, is probably not a potent inhibitor.[97] Trilostane is no longer available in the United States.

Aminoglutethimide, an anticonvulsant, inhibits the side chain cleavage of cortisol biosynthesis (cholesterol to pregnenolone). Dosage varies between 250 mg twice to three times daily. Initial falls in cortisol levels are usually overcome by an increase in ACTH. An early study in 39 patients showed a remission rate of 46%. Adverse effects are gastrointestinal symptoms, headache, dizziness, depression, and blurred vision. Aminoglutethimide is no longer available in the United States.

The hypnotic drug etomidate has a strong inhibitory effect that inhibits cholesterol chain cleavage and 11-deoxycortisol β-hydroxylase and it is the only parenteral and intravenous option for CS treatment.[98] Intravenously administered etomidate in a low nonhypnotic dose (0.03 mg/kg etomidate in a bolus injection, followed by constant infusion of 0.3 mg/kg/h for 24 hours) decreased

serum cortisol concentrations in a dose-dependent manner in subjects who were hypercortisolemic and eucortisolemic.[99]

Etomidate also has α-adrenergic activities, which may contribute to the cardiovascular stability in these patients.[100] Etomidate as a single line of therapy has been reported in patients with CS of other origins and use in 11 CD cases has been reported.[99,101–103] Because of very rapid onset of action, etomidate is a good option in severe emergent cases.

Etomidate has also been successfully used in patients (especially children) who developed liver enzymes abnormalities on ketoconazole.[104] Cortisol decrease can be seen within 12 to 24 hours of treatment[99,102] and glucocorticoid replacement to prevent adrenal insufficiency is warranted after 24 hours of etomidate infusion.[98] Adverse effects are dominated by sedation, pain at the infusion site, anaphylactic reactions, coughing, hiccups, nausea, myoclonus, and vomiting (www.drugs.com).[98]

LCI699 is an inhibitor of aldosterone synthase and 11β-hydroxilase, currently under investigation in a proof of concept study in patients with CD (www.clinicaltrials.gov).

Combination of adrenal steroidogenesis inhibitors

Recently, a triple drug combination as an alternative to urgent adrenalectomy has been discussed.[79] Eleven patients with CD with severe disease were simultaneously started on mitotane (3–5 g per 24 hour), metyrapone (3–4.5 g per 24 hour), and ketoconazole (400–1200 mg per 24 hour). UFC was noted to decrease very rapidly (within days). Clinical improvement permitted five patients to undergo pituitary surgery. Side effects were tolerable and no more so than with each medication alone (despite high doses).

Monitoring patients being treated with an adrenal steroidogenesis inhibitor

The fine line between eucortisolemia and abnormal cortisol can be hard to maintain in some cases.[6,22,23,25,30,44,105] Although still debatable, most authors agree that a mean normal serum or 24-hour UFC should be the aim of therapy. An initial dose should be slowly increased for tolerability. Later in the course of treatment, for most steroid synthesis inhibitors, it is necessary to increase the dose because the set point for negative feedback is higher in corticotroph tumors than in the normal pituitary. Frequent cortisol monitoring is necessary to diagnose adrenal insufficiency and breakthrough hypercortisolism in patients previously controlled (drug escape vs disease progression).

Another approach widely used is total blockade of glucocorticoid synthesis (hypocortisolism/adrenal insufficiency) and replacement with glucocorticoids. A possible drug holiday to evaluate CS remission in patients previously radiated is also recommended.

Glucocorticoid Receptor Blocker: Mifepristone

Mifepristone is a steroid that binds competitively to glucocorticoid, androgen, and progestin receptors (**Fig. 6**).[44] It blocks the action of cortisol by binding to the glucocorticoid receptor.[106]

Mifepristone use with CD was previously limited to just five cases (53 isolated or small series cases of mifepristone use to treat CS reported).[107–109] However, the recent SEISMIC study of mifepristone use (reviewed later) included 43 subjects with CD.[110]

Most patients with CS in the case series had received previous treatments, such as surgery, chemotherapy, or other therapeutic interventions, including a variety of anticortisolic drugs, without success. A majority of patients in these reports showed resolution of or significant improvement in somatic features of CS (buffalo hump, central obesity, moon facies, peripheral edema, striae). Many showed improvements in blood glucose levels and diabetes, including reductions in the use of antidiabetic medications or changing from insulin use to oral antidiabetic drugs. Improvements in depression and rapid resolution of psychiatric symptoms were also frequently reported.

Although mifepristone was used previously to treat other forms of CS,[109] the first CD case was reported in 2001.[108] The patient noticed a significant improvement in symptoms with heart failure amelioration and resolution of severe depression. Furthermore, diabetes control improved (HbA_{1c} decreased from 10.4% to 6.9%). Castinetti and colleagues[107] reviewed four patients with CD treated with mifepristone: rapid improvement of clinical signs was observed in three patients and

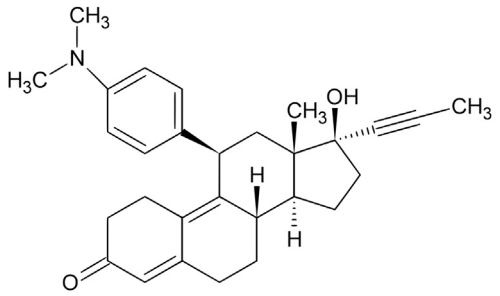

Fig. 6. Chemical structure of mifepristone.

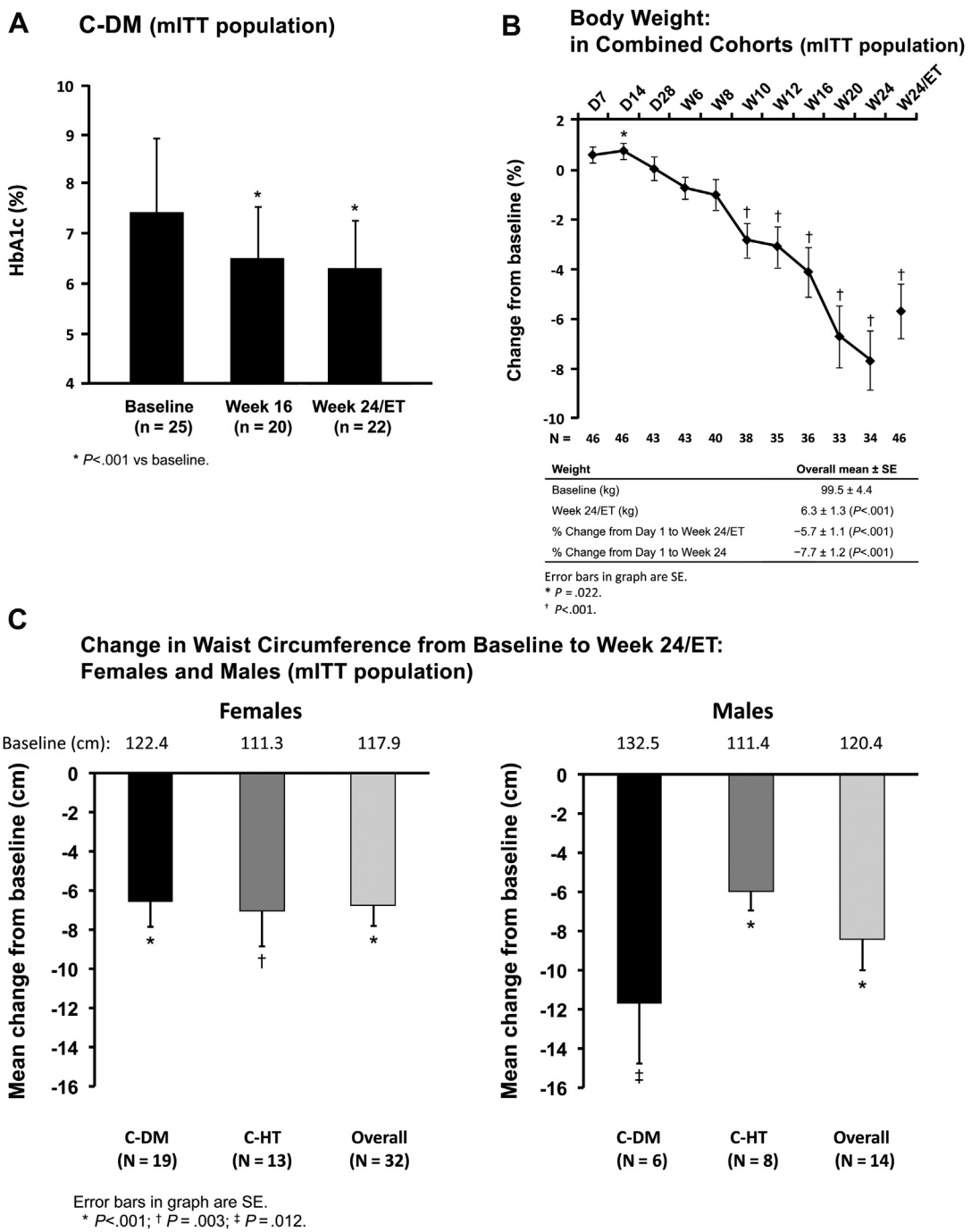

Fig. 7. (*A*) Changes in glucose-related outcomes. HbA_{1c} significantly decreased from baseline to week 24/early termination (*P*<.001). Data shown as mean ± SD. (*B*, *C*) Changes in weight and body composition. Results demonstrated a significant reduction in body weight from baseline to week 24/early termination (*P*<.001). Data shown as mean ± SE. To multiply insulin values to pmol/L multiply by 6.945. C-DM, patients with CS and type 2 diabetes/impaired glucose tolerance; C-HT, patients with CS and a diagnosis of hypertension; ET, early termination; HbA_{1c}, glycated hemoglobin A_{1c}; MITT, modified intent to treat. (*Adapted from* Fleseriu M, Biller BM, Findling JW, et al. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrinol Metab 2012;97(6):2039–2049; with permission.)

psychosis improved in 1 week in one patient. Cortisol and ACTH increases were observed in all patients (as expected by physiologic mechanism). Mifepristone dose ranged from 400 to 2000 mg/d over 6 to 24 months.

A serious potential side effect of mifepristone treatment is adrenal insufficiency. Adrenal insufficiency (hypotension) and signs of adrenal insufficiency (nausea, vomiting, or lethargy without hypotension) were noted for some patients: these episodes responded to dexamethasone treatment. The most commonly reported adverse effect was new or worsening hypokalemia, which responded to large doses of supplemental potassium and spironolactone.

In a recent 24-week multicenter, open-label trial in 50 subjects with CS that included 43 subjects with CD who had failed multimodal standard therapy, mifepristone was studied at a dose of 300 to 1200 mg daily (SEISMIC study)[110,111]; at the final study visit, mean dose was 732 ± 366 mg/d. Twenty-two subjects received the maximum dose of 1200 mg/d. The study included two groups: subjects with glucose intolerant or diabetes and subjects who had a diagnosis of hypertension but had a normal glucose tolerance. Diabetes control improved significantly, from a mean (± SD) baseline HbA_{1c} of 7.43 ± 1.52% to 6.29 ± 0.99% at the end of the study despite concomitant decreases in antidiabetes medications (**Fig. 7**A). Furthermore, mean (± SE) body weight change from baseline (99.5 kg) to week 24/early termination was −5.7 ± 7.4% (see **Fig. 7**B) (24 patients lost ≥5%, 12 of whom lost ≥10%, but 10 patients gained an average of 3.6 ± 3.9%). Waist circumference also decreased significantly by 6.8 ± 5.8 cm in women and 8.4 ± 5.9 cm in men (see **Fig. 7**C). In the hypertensive group, 38% of subjects had a change of at least 5% in diastolic blood pressure over baseline. Overall, 87% of the subjects had significant improvement in clinical status. Insulin resistance, depression, cognition, and quality of life also improved. Common adverse events were fatigue, nausea, headache, low potassium, arthralgia, vomiting, edema, and endometrial thickening in women. Adrenal insufficiency was reported in only two subjects, but mifepristone was decreased or interrupted and glucocorticoids were administered in several cases.[111] Because of mifepristone's mechanism of action, blocking the glucocorticoid receptor, cortisol measurements would not be reliable for any assessments (either for efficacy or adrenal insufficiency). Hypokalemia and edema may develop because of excess mineralocorticoid effect, but seem to respond well to potassium and mineralocorticoid antagonist medications (ie, spironolactone, epleronone).

Although not providing a cure, mifepristone treatment over 24 weeks diminishes the clinical impact of hypercortisolism and improves the associated cardiometabolic, psychiatric, and somatic abnormalities associated with the syndrome. Notably, the psychiatric and metabolic comorbidities may resolve rapidly and can dramatically improve patient's clinical status.[94,107] Longer-term studies are needed to assess benefit-risk ratio profile with prolonged treatment.

Combination Treatment Between Drugs with Different Mechanisms of Action

Several of the aforementioned drugs can be used as a single therapy; however, in general results are improved when drugs are used in combination. A combined treatment with ketoconazole and octreotide was reported to have additive effect in improving clinical features and reducing cortisol production in three out of four patients with severe ACTH-dependent hypercortisolism.[112]

Subsequently, combined treatment of SRLs and a dopamine agonist in a patient with no response to either agent also supports the hypothesis that somatostatin and dopamine receptor interact and that agonists may potentiate actions.[113] Some preliminary data also suggested a potential use of dopamine agonists alone or in combination with ketoconazole.[62,85] Feelders and colleagues[114] combined all of the aforementioned drugs in an 80-day trial in 17 patients with CD: pasireotide monotherapy induced UFC normalization in five patients with pasireotide. In nonresponsive patients, cabergoline was added and normalized in an additional four patients. The addition of low-dose ketoconazole increased the number of patients with a complete response to 88% after a further 2 months. Low doses of each therapy could allow also for fewer adverse events.

SUMMARY

The incidence of CD could be higher than previously thought. Severe complications (central adiposity, cardiovascular, diabetes, neuropsychiatric, bone disease) are a challenge if the disease is left untreated. Mortality is increased overall; however, results improve after treatment. This emphasizes the need for individualized, multidisciplinary management to normalize hypercortisolemia or manage devastating effects. Morbidity can persist even after remission.

Recently approved medications and ongoing research studies that involve innovative medical therapeutic agents, and strategies targeting the corticotroph adenoma itself, or that block the

effects of cortisol in the periphery, provide hope for future treatment options.

ACKNOWLEDGMENTS

The author thanks Shirley McCartney, PhD, for professional assistance with the manuscript, and Andy Rekito, MS, for illustrative services.

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