

Treatment of Cushing disease: overview and recent findings

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Abstract: Endogenous Cushing syndrome is an endocrine disease caused by excessive secretion of adrenocorticotropin hormone in approximately 80% of cases, usually by a pituitary corticotroph adenoma (Cushing disease [CD]). It is a heterogeneous disorder requiring a multidisciplinary and individualized approach to patient management. The goals of treatment of CD include the reversal of clinical features, the normalization of biochemical changes with minimal morbidity, and long-term control without recurrence. Generally, the treatment of choice is the surgical removal of the pituitary tumor by transsphenoidal approach, performed by an experienced surgeon. Considering the high recurrence rate, other treatments should be considered. Second-line treatments include more radical surgery, radiation therapy, medical therapy, and bilateral adrenalectomy. Drug treatment has been targeted at the hypothalamic or pituitary level, at the adrenal gland, and also at the glucocorticoid receptor level. Frequently, medical therapy is performed before surgery to reduce the complications of the procedure, reducing the effects of severe hypercortisolism. Commonly, in patients in whom surgery has failed, medical management is often essential to reduce or normalize the hypercortisolemia, and should be attempted before bilateral adrenalectomy is considered. Medical therapy can be also useful in patients with CD while waiting for pituitary radiotherapy to take effect, which can take up to 10 years or more. So far, results of medical treatment of CD have not been particularly relevant; however, newer tools promise to change this scenario. The aim of this review is to analyze the results and experiences with old and new medical treatments of CD and to reevaluate medical therapies for complications of CD and hypopituitarism in patients with cured CD.

Keywords: ketoconazole, somatostatin analogs, dopamine agonists, rosiglitazone, Cushing disease, glucocorticoids, hypopituitarism

Introduction

Endogenous Cushing syndrome is an endocrine disease caused by excessive secretion of adrenocorticotropin hormone (ACTH) in approximately 80% of cases, usually by a pituitary corticotroph adenoma (Cushing disease [CD]), less often by an extrapituitary tumor (ectopic ACTH syndrome), and very rarely by an ectopic corticotropin-releasing hormone – secreting tumor. ACTH-independent Cushing syndrome, accounting for about 20%, is due in most instances to an adrenal tumor, or more rarely, macronodular adrenal hyperplasia, primary pigmented nodular adrenal disease (either as isolated disease or as a part of Carney complex), or McCune–Albright syndrome.^{1,2}

In CD, elevated ACTH secretion results in excess adrenal gland cortisol secretion. The normal cortisol feedback mechanism of the hypothalamic-pituitary-adrenal axis is disturbed, with loss of circadian rhythm and excess cortisol production, resulting

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in hypercortisolism. Clinical features of hypercortisolism include weight gain, severe fatigue and muscle weakness, high blood pressure, depression, cognitive impairment, purplish skin striae, easy bruising, loss of libido, diabetes, hirsutism, acne, and menstrual disorders. The nonspecificity and high prevalence of clinical symptoms in patients without the disorder complicate the diagnosis of Cushing syndrome and also the differential diagnosis between the different causes of hypercortisolism.¹ For this reason, efficient screening and confirmatory procedures are essential before considering therapy. On the other hand, in untreated cases, morbidity and mortality rates are significantly elevated compared with those in normal subjects especially for the high cardiovascular and osteoporotic risk.^{3–8}

The goals of treatment of CD include the reversal of clinical features, the normalization of biochemical changes with minimal morbidity, and long-term control without recurrence.⁹

CD is caused by an ACTH-secreting tumor in the majority of cases, and so, optimal treatment is surgical resection by selective adenomectomy. In the event of failure after initial pituitary surgery or relapse after a period of remission, the second-line therapeutic options include repeated pituitary surgery, radiotherapy, or bilateral adrenalectomy. Finally, medical therapy may have a primary or adjunctive role in some cases. This review will focus on surgical treatment of CD, on therapies in case of persistent disease after transsphenoidal surgery (TS), and on medical management of CD.

Surgical treatment of CD

The first-line treatment of CD is the surgical removal of the pituitary tumor by transsphenoidal approach, performed by an experienced surgeon. Repeated TS may be undertaken if disease persists after initial surgery as soon as persistent disease is evident, but a delay of 4–6 weeks may be required to confirm the need for reoperation.⁹ The transsphenoidal microsurgery is still the most widely used technique; there are still less data available on outcome in entirely endoscopic surgery.⁹ However, the excellent view of the surgical field during endoscopic TS seems to provide an advantage in case of altered anatomy in repeated surgery.¹⁰

Efficacy

Remission rates in patients with microadenoma are in the range of 65%–90%. The recurrence rates are 5%–10% at 5 years and 10%–20% at 10 years. In patients with macroadenoma, remission rates are lower (<65% in most series), and recurrence also occurs sooner than in those with microadenoma (mean of 16 months vs 49 months).^{11,12}

If an adenoma cannot be located in sellar exploration, total or partial hypophysectomy may be indicated, but there is consensus that it may induce remission less often than a selective tumor resection.⁹ The rate of success is also lower in repeated TS than that seen after the initial surgery;⁹ it has been shown to be effective in approximately 50%–70% of patients in a limited number of specialized centers.¹³

Prognostic factors

Favorable prognostic factors for successful surgery include magnetic resonance imaging (MRI) detection of the microadenoma, a well-defined tumor that is not invading either the basal dura or the cavernous sinus, histological confirmation of ACTH-secreting tumor, low postoperative serum cortisol levels, and long-lasting adrenal insufficiency after surgery.^{9,11,12,14}

Safety

The most common complications of TS are diabetes insipidus, cerebrospinal fluid (CSF) leakage, vascular complications (occlusion and bleeding), and hypopituitarism. Total or partial hypophysectomy is associated with higher complication rates than selective tumor resection.^{9,12,15} Particularly, CSF leakage has been reported to occur more frequently during repeated TS than during the initial TS; this could depend on postoperative changes such as scar tissue but also as a result of a more aggressive surgical procedure in a usually small sella with a concave diaphragm.¹⁰ The higher rates of hypopituitarism after repeated TS can be expected because additional pituitary tissue is removed, even if the risk of hypopituitarism seems to be lower than reported rates several years after radiotherapy.¹⁶

Radiotherapy

In case of persistence or relapse of the disease, radiotherapy could be used. Fractionated external beam radiotherapy or stereotactic radiosurgery (SR) achieved control of hypercortisolism in approximately 50%–60% of patients within 3–5 years.^{17–20} Long-term follow-up is necessary to detect relapse, which can occur after an initial response to both types of radiotherapy. To date, comparison of SR with fractionated radiotherapy appears difficult due to different indications (such as, SR should presumably be reserved for patients with a small tumor volume and well delineated on MRI) and differences in length of follow-up. A recently reported²¹ series of patients with long-term follow-up (mean 96 months) after SR showed the following: (1) lower antisecretory efficacy of SR, (2) lower risk of adverse effects of SR, mainly in terms

of hypopituitarism, and (3) a risk of late recurrence after SR, as opposed to conventional radiotherapy.

It is well documented that pituitary radiation reduces the risk of tumor growth (facilitated by bilateral adrenalectomy) but not in all patients emphasizing the need for continued regular monitoring by MRI studies.

The main drawbacks of both procedures are the slow onset of a beneficial effect, which requires effective antisecretory drugs during this period, the risk of hypopituitarism, and the potential for damage to the brain, optic apparatus or cranial nerves.¹⁷ The risk of second tumor formation after pituitary radiation is considered to be in the range of 1%–2% with conventional radiotherapy.²² Studies with a more prolonged follow-up will be necessary for defining the risk of second tumor after SR. The reports^{19,23} of development of cranial nerve deficit and visual loss after a second SR treatment suggest caution in repeating this procedure.

Bilateral adrenalectomy

Bilateral adrenalectomy is a definitive treatment that provides immediate control of hypercortisolism, and the morbidity can be minimized by the use of endoscopic approaches. However, since it determines a condition of permanent hypoadrenalism, it requires careful education and evaluation of the patient relatively to the need for lifelong glucocorticoid and mineralocorticoid replacement therapy.²⁴ Moreover, because of the risk of developing Nelson syndrome, a corticotroph tumor progression, MRI scans, and ACTH evaluation have to be performed regularly in adrenalectomized patients.²⁵

The second-line treatment for persistent hypercortisolism should be individualized but, generally, bilateral adrenalectomy may be indicated in patients with persistent hypercortisolism despite medical therapy or with intolerance to pharmacological agents or as an alternative to long-term medical treatment after pituitary radiotherapy and finally in women who wish to maintain fertility.⁹

Medical management of CD

At odds to other pituitary adenomas such as prolactinomas²⁶ or growth hormone (GH)-secreting adenomas²⁷ in which medical treatment has historically or more recently gained a significant space, in CD, medical treatment is traditionally thought to have a marginal role. Nevertheless, there are numerous circumstances in which medical treatment of CD may be indicated. In fact, medical therapy is performed frequently before surgery to reduce the anesthesiological risk of the procedure, controlling the metabolic effects of severe

hypercortisolism in analogy to what is done in the patients with acromegaly.²⁸ Moreover, in patients in whom surgery has failed to control the disease, medical management is often essential to reduce or normalize hypercortisolemia, and should be performed before considering bilateral adrenalectomy. Medical therapy can also be useful in patients with CD while waiting for the complete effect of pituitary radiotherapy (that may take up to 10 years or even more). Finally, it is helpful as a palliative modality in rare CD patients with metastatic disease that is more common with cortisol-secreting adrenal cancer.²⁹

Several drugs may affect adrenal function. They can be schematically divided into two types: adrenolytic agents and neuromodulatory agents (Tables 1 and 2). Of these, the former are still the most successful and therefore widely used, whereas the latter agents are currently undergoing active research.

Adrenolytic agents

Ketoconazole

Ketoconazole is an imidazole derivative, which was originally developed as an oral antifungal agent. It is an inhibitor of sex-steroid and cortisol production by its action on C17–20 lyase and 11 β hydroxylase, respectively. It also inhibits 17-hydroxylase and 18-hydroxylase activities.³⁰ Treatment is usually started at a dose of 200 mg twice daily, which may be increased up to 1,200 mg/d in four divided daily doses.^{31–33}

Efficacy

The clinical signs and symptoms of hypercortisolism, including hypertension, hypokalemia, and diabetes mellitus are rapidly reversed, so antihypertensive and hypoglycemic drugs can often be discontinued. A meta-analysis of eight trials, involving different series of patients with CD treated with ketoconazole (dose range 400–1,200 mg daily), reported an average remission rate of 70% (range, 25%–93%).³⁴

Side effects

Reversible elevation of hepatic serum transaminases occurs in approximately 5%–10% of patients, with incidence of serious hepatic injury in approximately 1 of 15,000 cases. Histological changes can vary from predominantly cholestasis to extensive hepatocellular necrosis. Other adverse effects include skin rashes and gastrointestinal upset, and one must always be aware of the possibility to cause adrenal insufficiency.³⁵ Owing to its sex-steroid inhibitory action, ketoconazole is particularly useful in women with hirsutism, which may be worsened by metyrapone. On the other hand, gynecomastia

Table 1 Drugs with adrenolytic properties used in treatment of CD

Agent	Doses	Results/peculiar effects	Side effects/limits
Metyrapone	750–6,000 mg/daily	Effective	Hypoadrenalism, nausea, abdominal pain, hirsutism, acne No longer available in United States/compassionate use in Europe
Ketoconazole	400–1,200 mg/daily	Effective Slow onset of action	Gastrointestinal upset, rashes, elevation of hepatic serum transaminases, gynecomastia, reduced libido in men
Aminoglutethimide	250 mg/2–3 times daily	Less efficient in CD compared with the other causes of CS, often used as an adjunct to metyrapone	Self-limited pruritic rash, nausea, somnolence, dizziness, blurred vision, hypothyroidism, several potential medication interactions Cholestasis and bone marrow suppression are rare side effects No longer available
Mitotane	500 mg–12 g/daily	Effective (commonly used in cancer) Gradual dose titration, taken during meals	Adrenal insufficiency, gastrointestinal upset, neurological disturbances, elevation of hepatic enzymes, hypercholesterolemia, hyperuricemia, gynecomastia, prolonged bleeding time, change in hormone-binding globulins, teratogenicity
Etomidate		Effective	Case reports in pediatric population

Abbreviations: CD, Cushing disease; CS, Cushing syndrome.

and reduced libido in men may be unacceptable. One further potential advantage is its inhibition of cholesterol synthesis described in a series of patients with Cushing syndrome.³³

Metyrapone

Metyrapone inhibits the enzyme 11 β -hydroxylase by blocking the production of cortisol from 11-deoxycortisol in the adrenal gland. The resultant relative decrease in cortisol may stimulate further ACTH secretion, increasing adrenal androgen and

aldosterone precursors with weak mineralocorticoid activity. The drug is often started at thrice-daily doses of 250 mg, with titration up to a maximum of 6 g/d.

Efficacy

The inhibitory effect of metyrapone overcomes the increased drive to produce cortisol and has shown efficacy over an extended period of treatment.³⁶ In a large study³⁷ including 53 patients with CD, a short-term control of mean serum

Table 2 Drugs centrally active (reduction of ACTH secretion) with therapeutic potential in CD

Agent	Doses	Results/peculiar effects	Side effects/limits
Somatostatin analogs			
Octreotide	100–300 µg/daily	Ineffective in clinical studies	Gastrointestinal discomfort, gall stones, hyperglycemia, GH deficit?
Pasireotide	600 µg twice daily	Phase 2 study shows promising results	
Dopamine agonists			
Bromocriptine	3–30 mg/daily	Poor long-term results but renewed interest	Nausea and postural hypotension Cardiac valve dysfunction?
Cabergoline	1–7 mg/wk	More efficacious than bromocriptine	Postural hypotension Cardiac valve dysfunction?
Histamine and serotonin antagonists			
Cyproheptadine	4–24 mg/daily	Small series, rarely effective	Sedation, weight gain
5-HT2 antagonist			
Ritanserin		No sustained effects in most patients	
PPAR-γ receptor agonists			
Rosiglitazone	4–16 mg/daily	In vitro success not reproduced in clinical practice	
Pioglitazone	45 mg daily		

Abbreviations: ACTH, adrenocorticotropin hormone; CD, Cushing disease; GH, growth hormone; PPAR- γ , peroxisome proliferator-activated receptor- γ ; 5-HT, 5-hydroxytryptamine.

cortisol level (≤ 400 nmol/L) was obtained in 75% of patients compared with effective long-term control in 83% of 24 patients who were given metyrapone (mean, 2,250 mg/d; median, 27 months) following pituitary irradiation.

Side effects

The main side effects are hirsutism, acne (which can clearly be problematic in women), dizziness, and gastrointestinal upset. Hypoadrenalism remains the most important potential problem, and careful monitoring of treatment and education of the patient is required. Hypokalemia, edema, and hypertension due to raised mineralocorticoids are infrequent but may require cessation of therapy.^{32,37}

Of note, metyrapone is not commercially available but can be provided for compassionate use by contacting the manufacturer directly.

Aminoglutethimide

Aminoglutethimide, which is no longer available in the United States and Europe, often used at a dose of 250 mg 2–3 times daily, prevents conversion of cholesterol to pregnenolone. Thus, it inhibits not only cortisol production but also estrogen and aldosterone production.

Efficacy

In the largest published study of 66 patients with Cushing syndrome,³⁸ a favorable response was seen in 14 of 33 patients with CD. However, aminoglutethimide seems to be less efficient in CD compared with the other causes of Cushing syndrome. This may be due to an increase in ACTH overcoming the enzymatic blockade or by hepatic enzyme induction that increases its own metabolism leading also to tolerance with continued treatment and explaining some side effects.³² Because of its limited efficacy, aminoglutethimide is now most often used as an adjunct to metyrapone for reducing the doses and, thus, the toxicity of the drug.³⁹

Side effects

The primary side effect is a generalized, self-limited pruritic rash that is usually manageable with antihistamine drugs. Nausea, somnolence, dizziness, and blurred vision may occur. As the drug blocks thyroid hormone synthesis, hypothyroidism is a well-known side effect. Cholestasis and bone marrow suppression are rare side effects. Being a strong inducer of several cytochrome P450 enzymes, aminoglutethimide may have several potential interactions with other medications. Because this medication increases the metabolism of dexamethasone but not that of hydrocortisone, the latter is often used if steroid replacement is needed.⁴⁰

Mitotane

Mitotane is often started at 250–500 mg nightly with slow escalation of the dose up to 4–12 g/d. This drug inhibits 11 α -hydroxylase, 18-hydroxylase, 3 α -hydroxylase, hydroxysteroid dehydrogenase, and several cholesterol side-chain cleavage enzymes. At doses greater than 4 g/d, it has toxic effect because its metabolite binds macromolecules in adrenal cortical cell mitochondria, leading to their destruction and cellular necrosis. Because of this property, its primary use is in patients with adrenocortical carcinoma.⁴¹

Efficacy

In a large historical study⁴² including 46 CD patients receiving mitotane from 4 to 12 g/d, remission occurred in 38 cases (83%) in 8 months. All 16 patients who received both mitotane and pituitary radiotherapy were controlled. In another study⁴³ with adjunctive radiotherapy, remission was observed in 29 of 36 patients (81%), and in 17 patients (47%) long-term mitotane therapy was not necessary. In this last study, lower-dose mitotane regimen (up to 4 g/d) was used to reducing side effects. These studies not only highlighted the slow onset of action of mitotane but also showed that the adrenolytic effect can persist even after the drug is stopped.

Side effects

Side effects of this medication may limit its use. In fact, with doses as high as those used in carcinoma, the incidence of adrenal insufficiency and adverse effects, particularly gastrointestinal upset (57%), is significant. Of note, patients who undergo mitotane treatment, similarly to patients submitted to bilateral adrenalectomy, are at risk of developing Nelson syndrome if they do not receive pituitary radiotherapy.³⁶ Other side effects include neurological disturbances (ataxia, vertigo, confusion, and language impairment), elevation of hepatic enzymes, hypercholesterolemia, hyperuricemia, gynecomastia, prolonged bleeding time, and change in hormone-binding globulins.³² Hypercholesterolemia responds to treatment with 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors.⁴⁴ Finally, the drug is contraindicated in pregnant women for its teratogenicity.⁴⁵

Etomidate

Etomidate, a commonly used short-acting intravenous anesthetic, is a potent inhibitor of 11 α -hydroxylase and an inhibitor of 17 α -hydroxylase.

There have been a number of case reports on the successful use of etomidate in controlling hypercortisolemia in seriously ill patients with CD even in the pediatric population.^{46–48}

Neuromodulatory agents

As stated above, for several reasons (mechanism of action and side effects), adrenolytic agents are more suitable for short-term adjunctive treatment. Therefore, the search for more “pathogenetic” drugs, which thus may act on ACTH secretion at the pituitary adenoma level without interfering with other hormone synthesis and may even be used as primary treatment, is still open.

In this vein, it is worthwhile to dedicate a specific section of this review to neuromodulatory centrally active agents such as somatostatin (SS) analogs and dopamine agonists (DAs).

SS analogs

Preclinical studies: SS receptors in normal corticotroph cells and in vitro studies with SS analogs in corticotroph cell lines and adenomas

Rat pituitary corticotrophs express multiple somatostatin receptors (sst), including sst2 and sst5,⁴⁹ but treatment of cultured rat corticotrophs with native SS-14 does not result in inhibition of ACTH release.⁵⁰ However, SS-14 is able to decrease ACTH release when rat pituitary cells are cultured in glucocorticoid-free media.⁵¹ Therefore, it can be hypothesized that the presence of glucocorticoids reduces the inhibitory effects of native SS and traditional SS analogs on ACTH release through the down regulation of the SS binding sites.⁵² A number of studies have indicated that, in the murine AtT-20 cells, sst2 and sst5 are principally involved in the regulation of ACTH release. More recently, it was found that sst5-targeting agonists were more effective than sst2-targeting agonists in inhibiting ACTH release; this could depend on dexamethasone decreasing sst2 but not sst5 expression. In fact, octreotide (that binds preferentially sst2 but only modestly sst5), but not pasireotide (a universal ligand with high binding affinity for sst1, sst2, sst3, and sst5), lost most of its ACTH-inhibiting potential with glucocorticoid pretreatment⁵³ or in patients with CD in vivo.⁵⁴ Two studies^{55,56} investigated the effects of SS analogs in human corticotroph adenoma tissues; a superior ACTH inhibition by pasireotide as compared with octreotide⁵⁵ and a dissociation in some adenomas between the antisecretory and antiproliferative effects of pasireotide⁵⁶ were reported similar to what is observed in acromegaly.^{57,58}

Efficacy in clinical studies

In clinical studies, the currently available SS analogs, octreotide and lanreotide, which are effective in the treatment of acromegaly,⁵⁹ are ineffective in CD.^{60–62} Many authors^{62–64} have found that, in Nelson syndrome, an expanding ACTH-producing pituitary adenoma after bilateral adrenalectomy

may respond to octreotide with reduction in circulating ACTH levels. This observation could be explained with the lack of glucocorticoid-induced down-regulation of sst2, as mentioned above.⁵²

A Phase II, proof of concept, open-label, single-arm, multicenter study of pasireotide in CD has been recently published.⁶⁶ Patients self-administered pasireotide 600 µg subcutaneously twice daily for 15 days at 9:00 AM and 9:00 PM. The selected dose was based on pharmacokinetic analysis. Dose adjustments were permitted for patients who were unable to tolerate the protocol-specified dose (150 µg per injection). The primary efficacy population consisted of 29 patients from a total of 39 patients recruited from 10 centers. At diagnosis, urinary free cortisol (UFC) had to be at least two times above the upper limit of normal. UFC levels decreased in 76% of patients but only 17% (5 of them) normalized UFC levels after 15 days. Overall, the mean UFC level decreased from baseline by 44.5%. In addition, reduction in serum cortisol and plasma ACTH was observed during the pasireotide treatment. There was a trend ($P=0.102$) toward a lower baseline UFC level being predictive of a response to pasireotide. There were no significant differences in baseline ACTH area under the curve (AUC_{0-8h}) values between UFC responders and nonresponders. A 1.8-fold higher plasma concentration and 1.3-fold higher plasma exposure of pasireotide were observed in UFC responders than in nonresponders suggesting a role of pasireotide exposure in determining response to treatment.

Safety and tolerability

The most common events with pasireotide were drug-related gastrointestinal disorders (54% of patients), mainly diarrhea (44%), nausea (23%), and abdominal pain (18%). Hyperglycemia, another potential effect of SS analogs,⁶⁷ occurred in 14 patients (36%) and 1 of them, with a pre-existing history of diabetes mellitus, discontinued the treatment. Analysis of insulin and glucagon levels at baseline vs during treatment indicated that pasireotide administration was followed by initial suppression of insulin but did not significantly influence glucagon release.

Another potential problem of pasireotide in CD might be its effects on GH and insulin-like growth factor (IGF)-1 levels in CD. In preclinical studies, pasireotide significantly decreased GH and IGF-1 levels. In patients with CD, hypercortisolism per se causes a relative GH deficiency (GHD),^{68,69} and therefore, these patients may be at greater risk to become GH deficient. Future clinical studies are needed to clarify this aspect.

Dopamine agonists

Preclinical studies: DA receptors in normal corticotroph cells and in vitro studies with DA in corticotroph adenomas

In humans, no conclusive data exist whether ACTH release is directly regulated by DA receptors in normal corticotroph cells.⁷⁰ On the other hand, in rats, it is known that the intermediate lobe in the pituitary is under tonic inhibitory control of the hypothalamic dopaminergic neurons.⁷¹ In humans, the intermediate lobe is a rudimentary structure although it has been suggested to maintain some biological functions;^{72,73} corticotroph adenomas arising from the intermediate lobe may be more likely to respond to the classical dopaminergic agent bromocriptine.⁷⁰

In 2004, Pivonello et al⁷⁴ showed that the majority (80%) of human corticotroph adenomas express the D₂ receptors as demonstrated by immunohistochemistry and reverse transcriptase–polymerase chain reaction. Moreover, functional studies in vitro correlated very well with the D₂ expression data, and adenomas with high D₂ expression responded well to either bromocriptine or the newest dopaminergic cabergoline with acute inhibition of ACTH release by 43% to 60%.

Efficacy in clinical studies

Although initial reductions in ACTH levels were evident in almost half of patients with CD in response to bromocriptine administration, a sustained response occurred only in a small percentage of patients.⁷⁰ Compared with bromocriptine, cabergoline binds with even greater specificity and affinity to D₂ receptors and has a longer duration of action. In the study by Pivonello et al⁷⁴ 20 patients with CD were treated with cabergoline at a dose of 1–3 mg/wk for 3 months with a significant decrease in UFC in 60% of the patients and even complete normalization in 40% of them. Several other case reports suggested that at least in some patients with CD, cabergoline could control cortisol hypersecretion.^{75,76} More recently, Pivonello et al⁷⁷ in the extension of a previously reported preliminary study, evaluated for the first time the results of chronic cabergoline treatment in CD. The results of the study demonstrated that a 24-month treatment with cabergoline, at doses between 1 and 7 mg/wk, induced or maintained control of cortisol secretion in 40% and induced tumor shrinkage in 20% of a group of 20 patients with CD, improving hypertension and glucose tolerance in the majority of patients, regardless of the normalization of cortisol secretion.

Safety and tolerability

Concerning the long-term study with cabergoline,⁷⁷ no severe side effects were documented. However, hypotension

associated with severe asthenia was observed in two patients, who stopped the drug after 12 and 18 months of treatment. A transient moderate asthenia was registered in four patients, whereas a transient mild dizziness with nausea was reported by another patient but these latter side effects did not require treatment withdrawal. It is noteworthy that no significant cardiac valve dysfunction was found in this study, with the exception of a slight worsening of tricuspid regurgitation in one patient. This is important because high-dose, long-term cabergoline therapy has been recently described to be associated with an increased prevalence of cardiac valve insufficiency^{25,26} not only in Parkinson disease.⁷⁸ However, because of the short period of follow-up so far available (maximum 2 years), no firm conclusion on this side effect of cabergoline in CD may be drawn.

Combined treatment with SS and DA agonists

Considering the presence of both sst and DA receptors in human corticotroph adenomas, the cotreatment with SS analogs and DA agonists (pasireotide + cabergoline) or perhaps, in the future, the administration of SS–DA chimeric compounds, such as BIM-23A760, already tested in vitro in GH-secreting adenomas, seem to be a reasonable approach. Very recently, pasireotide monotherapy has been shown to induce sustained normalization of the level of UFC in 5 of 17 patients studied (29%). The addition of cabergoline normalized UFC values in another 4 of 17 patients (24%). At day 60, 8 of 17 patients (47%) still had elevated UFC levels with the pasireotide–cabergoline combination, although a trend toward normalization was observed in all except one, with a mean decrease of 48% ± 6% in the level of UFC.⁷⁹

PPAR-γ agonists

In 2002, the nuclear hormone receptor, peroxisome proliferator-activated receptor-γ (PPAR-γ), was identified in ACTH-secreting pituitary tumors. Development of murine corticotroph tumors, generated by subcutaneous injection of ACTH-secreting AtT-20 cells, was prevented in 4 of 5 mice treated with the PPAR-γ receptor agonist rosiglitazone, and ACTH and corticosterone levels were suppressed in all treated mice.⁸⁰

Efficacy and side effects

In a study of 10 patients, four prior to surgery, four following relapse after surgery, and two immediately after failed surgery treated with 4–16 mg of rosiglitazone for 1–8 months (median 3 months), and no consistent reductions in UFC levels were found.⁸¹

Side effects reported included edema, weight gain, somnolence, and increased hirsutism. In a larger study, 14 patients with active CD (7 untreated and 7 after unsuccessful surgery) were treated with 8–16 mg of rosiglitazone for 1–7 months.⁸² In six patients, 24-hour UFC was significantly lowered and two of them also noted clinical improvement at 7-month follow-up. Relatively, to side effects, one patient developed hypercholesterolemia. Although most studies used rosiglitazone, pioglitazone has also been tried;⁸³ in none of five patients with CD treated with pioglitazone, 45 mg for 30 days, any UFC responses were observed. Therefore, clinical trials of PPAR- γ agonists in CD have lead to disappointing results, unfortunately, failing to reproduce the success observed in the *in vitro* and mouse model. It should be recalled that human corticotroph tumors have a different proliferative potential than murine AtT-20 cells, as the latter quickly replicate and grow when implanted into nude mice. Conversely, human pituitary ACTH-secreting tumors do not exhibit such a pronounced growth pattern and indeed are typically small in size even in patients with long-standing CD. If the ACTH-lowering effect of rosiglitazone is primarily due to its antiproliferative effect, a long time frame would be necessary for a decrease in ACTH levels to occur in human pituitary tumors. Furthermore, rosiglitazone might be more effective in ACTH-secreting macroadenomas than in microadenomas. This possibility remains to be investigated as none of the patients with CD included in clinical trials presented with macroadenoma. An additional consideration is that the dose of rosiglitazone used in clinical studies was far less than that used in mice with experimental CD,⁸¹ which attained 10–50 fold greater concentrations of the drug. Finally, a potential concern for the long-term use of rosiglitazone in CD is its pro-osteoporotic effects already observed in diabetic patients.⁸⁴

Retinoic acid

The antiproliferative action and the ACTH and corticosterone inhibition induced by retinoic acid *in vitro* were confirmed *in vivo* in mice with experimental ACTH-secreting tumors and in dogs with CD. However, the efficacy of these treatments in patients with CD still needs to be tested in clinical trials.⁸⁵

Glucocorticoid receptor antagonists

Finally, in analogy with acromegaly where the peripheral GH antagonist pegvisomant has been successfully used,^{26,86} an antagonist to block the peripheral effects of glucocorticoids may be engineered for the future. So far, there is no significant experience reported with the glucocorticoid receptor antagonist mifepristone (RU 486) in CD, and assessment

of its efficacy in the absence of a biochemical marker is challenging.⁹ In a European retrospective study, clinical signs of hypercortisolism improved rapidly in three of four patients with CD treated with mifepristone but one developed hypertension and severe hypokalemia during the therapy.⁸⁷

Therapy for the complications of CD

Cardiovascular complications

Arterial hypertension is a common feature in CD (70%–80% of the patients) and may be the first sign of CD. Conventional antihypertensive therapy (thiazides, angiotensin-converting enzyme inhibitors, and calcium antagonists are generally considered as first choice) may be only partially effective, whereas the additional successful use of cortisol-lowering agents may improve blood pressure control.⁸⁸ Hypertension remits in most patients after successful treatment, but in some cases, it may persist probably because of microvessel remodeling and/or underlying essential hypertension.⁸⁹

Epidemiological studies show that 20%–30% of patients with CD have diabetes mellitus, whereas impaired glucose tolerance is reported in 30%–60% of them.⁹⁰ The impairment of glucose metabolism generally resolves with normalization of cortisol levels because hypercortisolism *per se* is the causative factor of hyperglycemia. However, treatment with SS analogs, as previously reported, may theoretically cause the appearance or the worsening of diabetes.⁶⁷ Diabetes should be controlled by oral hypoglycemic drugs or, more frequently, by insulin therapy.

The metabolic syndrome of CD associated with the hypercoagulability state determines an increased cardiovascular risk that may persist after cure and is the principal cause of death in CD patients with persistent hypercortisolism. In the absence of prospective randomized trials, there is general agreement that patients with CD should be given heparin during inferior petrosal sinus sampling and low-dose heparin treatment should be considered in the immediate perioperative period.¹

Osteoporosis

Several authors reported that glucocorticoid-induced osteoporosis is reversible.^{8,91} Patients with Cushing syndrome had a restoration of osteoblast activity, evaluated on the basis of increased osteocalcin levels, after 6 months of disease cure, without achieving any relevant changes in bone mineral density (BMD). Thereafter, remarkable improvement of BMD can be observed in almost all patients after a normalization period of cortisol levels lasting 12–36 months.⁹² Similarly, in a retrospective study of 17 patients with Cushing syndrome,

after several years of cure, normalization of BMD at lumbar spine and femoral neck was reported.⁹³

Moreover, bone impairment in patients with childhood and adulthood onset CD can be partly, but not completely, reversed 2 years after normalization of cortisol levels, suggesting that longer recovery times or additive therapeutic approaches are necessary to maximize peak bone mass in children and restore bone mass in adults with CD.⁹⁴

The mechanism of the recovery in BMD can only be speculative. Glucocorticoids rapidly and sharply increase bone resorption (this is considered the major contributor to the almost immediate increase in fracture risk caused by excess corticosteroid levels) but importantly, particularly in the long-term, they diminish bone formation rate.^{95,96} This latter effect as evaluated by circulating levels of osteocalcin is rapidly reversible with normalization of hypercortisolism. A second important contribution to this recovery may be the preservation of trabecular architecture despite trabecular thinning in steroid-induced osteoporosis, so the framework in which the osteoblasts can synthesize new bone is intact. This contrasts with the loss of trabeculae that occurs in other forms of osteoporosis.¹

In patients treated with ketoconazole after unsuccessful pituitary surgery, even when normalization of cortisol levels was achieved, BMD remained low; this finding could be in line with slow and difficult recovery of bone metabolism after cure of CD but, alternatively, could suggest an interfering effect of ketoconazole on bone metabolism.⁹⁷ Overall, it can be concluded that the recovery of bone loss is gradual, taking approximately 10 years to complete. In the meanwhile, patients with severe osteopenia are exposed to a high risk of fracture. Therefore, in these patients, the use of antiresorptive medications could be useful. In fact, recent data suggest that alendronate may induce a more rapid improvement in BMD than cortisol normalization alone, probably by restoring the balance between bone formation and resorption. In addition, alendronate treatment was also shown to be useful in patients with persistent postsurgical hypercortisolism as it prevented further bone loss.⁹⁸

Although there are no large prospective studies in patients with CD, additional therapies, such as calcium and vitamin D supplementation and sex hormone replacement in men or women with hypogonadism, may likely be beneficial.¹ New data on the use of anabolic therapies (parathyroid hormone and GH)^{99,100} in glucocorticoid-induced osteoporosis are encouraging and could be also prospectively applied to patients with endogenous hypercortisolism.^{101–103}

Considering that the risk of fractures persists sometime after cure of hypercortisolism, the decision to discontinue

antiresorptive therapy should be based at least on clinical monitoring and dual energy X-ray absorptiometry measurements.¹ However, because BMD is not a good predictor of fractures in CD, a spine X-ray could also be indicated.¹⁰⁴

Hypopituitarism in cured CD

Hypopituitarism is a well-known possible complication of surgery and radiotherapy for pituitary diseases. As previously stated, several treatments of CD may induce hypopituitarism. However, although the necessity of substitutive treatment of several tropin deficiency, including ACTH, is intuitive, there is still, for several reasons, interest and debate surrounding prevalence, diagnosis, and treatment of GHD. In fact, even subtle excess of glucocorticoids inhibits GH secretion,¹⁰⁵ indeed, GH secretion is impaired in both children and adult patients with CD.¹⁰⁶ In contrast, to what extent recovery of GH secretion follows the normalization of cortisol levels is less well established.¹⁰⁷ This uncertainty is due to the fact that patients were often tested shortly after remission of hypercortisolism, and remission was achieved by several treatment modalities, including radiation therapy, which is known to progressively impair anterior pituitary function over time. Further, patients cured from CD frequently do not normalize body weight and this may confound the interpretation of GH status.¹⁰⁸

Some studies reported the presence of GHD in a high percentage of CD after long-term remission of hypercortisolism obtained by surgery alone.¹⁰⁹ A retrospective cross-sectional study¹¹⁰ has been recently published with the comparison of cured patients with CD ($n = 684$, 74% women) and nonfunctioning pituitary adenoma (NFPA; $n = 2,990$, 39% women) treated for 3 years with GH after the diagnosis of GHD.^{111,112} The study showed a significant delay in GHD diagnosis in the CD group, who had a higher prevalence of hypertension, fractures, and diabetes mellitus. In untreated GHD, comorbidities, including impairment of quality of life, were more prevalent in patients with previous CD. Overall, both groups responded similarly to GH replacement, suggesting that patients with GHD due to CD may benefit from GH to the same extent as those with GHD due to NFPA. On the other hand, improvements in BMD occur later in patients with prolactinomas and CD treated with GH when compared with NFPA.¹¹³

Finally, when the long-term complications were considered, GH-treated patients with previous hypercortisolism showed an increased risk of metabolic syndrome, cardiovascular disease, and cerebrovascular disease as compared with GH-treated patients with previous NFPA.¹¹⁴

Conclusion

CD is a severe and complex clinical syndrome, which needs aggressive and possibly rapid curative treatment due to its long-term sequelae. Unfortunately, current therapeutic options do not achieve cure in a relevant part of patients even in the hands of the most specialized centers. Therefore, the search for new medical effective tools is still open, and already promising results have been obtained. Finally, these considerations emphasize the need of a careful follow-up and aggressive treatment of complications in CD particularly in patients with difficult control of the disease but also interestingly and somewhat paradoxically in patients with cured CD.

Disclosure

The authors report no conflicts of interest in this work.

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