ENDOCRINOLOGÍA Y NUTRICIÓN

REVIEW ARTICLE

New prospects for drug treatment in Cushing disease ☆

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Abstract Hypercortisolism induced by Cushing disease causes high morbidity and mortality.

The treatment of choice is pituitary surgery, but it often fails to achieve cure, and other treatment modalities (radiotherapy, bilateral adrenalectomy) may therefore be required. If these treatments are not effective or while waiting for their results, hypercortisolism should be controlled with drugs.

The classical drug treatments are those that act by inhibiting cortisol secretion by the adrenal gland (ketoconazole, metyrapone, mitotane, etomidate).

The preliminary results of a new drug (LCI699) which is a potent enzyme inhibitor of cortisol secretion have been reported.

A clinical trial of the safety and efficacy of mifepristone, a glucocorticoid receptor antagonist, has just been published.

The drugs deserving more attention today are those with a direct action on the tumor by inhibiting ACTH secretion: somatostatin analogs (pasireotide), dopamine agonists (cabergoline), PPAR-γ, and retinoic acid.

A special review is made of the available clinical trials with pasireotide and cabergoline.

Nuevas perspectivas en el tratamiento farmacológico de la enfermedad de Cushing

Resumen El hipercortisolismo que produce la enfermedad de Cushing es causa de alta mor-bimortalidad.

El tratamiento de elección es la cirugía hipofisaria pero con frecuencia no consigue la curación por lo que pueden ser precisas otras modalidades de tratamiento (radioterapia, suprarrenalec-tomía bilateral). Ante la falta de eficacia o en espera de los resultados de estos tratamientos se necesita del control del hipercortisolismo con fármacos.

Los tratamientos farmacológicos clásicos son los que actúan inhibiendo la secreción de cortisol por las suprarrenales (ketoconazol, metopirona, mitotano, etomidato). Recientemente se han presentado resultados preliminares de un nuevo fármaco (LCI699) que es un potente inhibidor enzimático de la secreción de cortisol.

Se acaba de publicar un ensayo clínico sobre seguridad y eficacia con el uso de mifepristona, un antagonista del receptor glucocorticoideo.

Los fármacos que en la actualidad están mereciendo más atención son aquellos con acción directa sobre el tumor inhibiendo la secreción de ACTH: análogos de la somatostatina (pasireótida), dopaminérgicos (cabergolina), agonistas del receptor PPAR-γ y el ácido retinoico.

Se hace una especial revisión de los estudios clínicos disponibles con pasireótida y cabergolina.

Introduction

Cushing's disease is most often caused by a microadenoma (less than 1 cm in size), and the resulting morbidity and mortality are therefore mainly related to elevated adrenocorticotropic hormone (ACTH) secretion and the resultant cortisol hypersecretion. The treatment of choice is pituitary surgery, which in the hands of experienced surgeons achieves remission in 65–90% of cases.[1] However, long-term recurrence may occur in up to 25% of cases.[2]

If surgery fails or recurrence occurs, the second option, apart from repeat surgery, is radiation therapy. Although this treatment has no immediate effect, it achieves normalization of cortisol levels in 50–60% of cases in the following three to five years. A disadvantage is the frequent occurrence of hypopituitarism, as well as the risk, not clearly established yet, of cerebrovascular and neurocognitive changes, and the possibility of inducing a second brain tumor.[1]

Bilateral adrenalectomy may also be considered because it achieves immediate control of cortisol hypersecretion, but it requires permanent replacement therapy and may induce Nelson's syndrome.

Medical treatment is needed to control hypercortisolism in various circumstances:

- Before surgery to decrease perioperative complications.
- When surgery is contraindicated due to age and/or significant comorbidity.
- When surgery fails or recurrence occurs.
- To control hypercortisolism while waiting for radiation therapy to take effect.

The various drug treatments available are classified into three groups depending on their action site: drugs acting upon the adrenal gland to inhibit steroidogenesis, drugs acting directly upon the pituitary tumor, and drugs blocking the glucocorticoid receptor.

This review will emphasize the data most recently reported on these treatment modalities, particularly for drugs with a direct action on the tumor, and will only briefly mention more traditional treatments which have already been reviewed in this journal.[3]

Drugs with inhibitory action on adrenal synthesis

The greatest experience of use has been obtained with drugs that inhibit cortisol secretion. These have been shown to be highly effective for the control of high cortisol levels and their clinical manifestations.

Ketoconazole

Ketoconazole is an antifungal drug which, in high doses, decreases the production of adrenal steroids through the inhibition of several enzymes such as 11-β-hydroxylase, 17-hydroxylase, and 18-hydroxylase. Multiple studies have shown the value of ketoconazole for the treatment of Cushing's disease.[4–6] At doses of 200–400 mg two or three times daily, rapid and sustained normalization of plasma and urinary free cortisol levels is achieved in 70% of cases. The most common side effects include gastrointestinal discomfort, pruritus, and liver function changes. In 5–10% of cases, there is transient transaminase elevation that resolves after drug discontinuation or dose decrease, or even despite treatment continuation. Another form of liver impairment is so-called symptomatic liver involvement, occurring in 1:15,000 patients. In any case, treatment with ketoconazole requires liver function monitoring. Other less common side effects include gynecomastia and hypogonadism, which are reversible upon treatment discontinuation or adjustment. Ketoconazole should be considered as the medical treatment of choice in most patients with Cushing's disease.[3,7]

Metyrapone

Metyrapone inhibits 11-β-hydroxylase, blocking the final step in cortisol synthesis. It has a rapid action, so that when taken at a dosage of 0.5–6 g/24 h divided into three daily doses, significant cortisol reduction is achieved in 2 h.[8] Its efficacy for disease control varies, ranging from 75% when assessed in the short term and 18% in long-term treatment. The side effects of metyrapone include dizziness, edema, hypokalemia, and nausea, but hirsutism and acne, caused by elevated adrenal androgen levels, are the most significant effects. Therefore, decreased effectiveness in the long term and the need to use other drugs to control hirsutism make metyrapone an alternative of little value for long-term treatment. By contrast, it has been shown to be useful for short-term treatment.[3,6,8–10]

LCI699

Like metyrapone, LC1699 is a potent inhibitor of 11-β-hydroxylase (CYP11B1), the enzyme that catalyzes the final step in cortisol synthesis.

Data from a preliminary study of 11 patients with Cushing's disease and urinary free cortisol levels more

than 1.5 times higher than the upper reference limit have recently been reported.[11] Treatment was started with 2 mg twice daily, and doses were gradually increased to 5, 10, 20, and 50 mg twice daily to normalize urinary cortisol levels. Treatment duration was 10 weeks.

Of the nine patients who completed the study, eight achieved normal urinary cortisol levels, requiring a mean dose ranging from 5 and 10 mg twice daily. The drug was usually well tolerated, and the most common side effects were fatigue (5 patients), nausea (4 patients), headache (3 patients, and moderate hypokalemia (4 patients).

Mitotane

Mitotane actions not only include an adrenocorticolytic action inhibiting the P450c11 and P450scc enzymes, but also mitochondrial destruction and necrosis of adrenal cells. It is therefore mainly used in patients with adrenal carcinoma. In Cushing's disease, the starting dose is 0.5 g at bedtime, with weekly increases of 0.5 g with meals until a final dose of 2 or 3 g/day is achieved. The start of action is slow (from 3 to 5 months). Mitotane circulating levels should be monitored to ascertain if the therapeutic dose is achieved without causing toxicity. Treatment duration ranges from 6 to 9 months. Since the time of start of cortisol reduction cannot be predicted, treatment should be combined with prednisone 5 mg. Glucocorticoid treatment should be continued for several weeks to months after mitotane discontinuation. Although 80% of patients respond to treatment, long-term relapse after drug discontinuation occurs in up to 60%. Because of this, and due to the possibility of developing Nelson's syndrome, mitotane should be used in Cushing's syndrome for patients previously or concomitantly being treated with pituitary radiation therapy. Side effects, mainly gastrointestinal and neurological, are common. This, combined with the complex drug management required, imposes serious limitations on the use of mitotane.[3,9,10]

Etomidate

Etomidate is an imidazole derivative used as a short-acting anesthetic by the intravenous route. It is a potent inhibitor of 11-β-hydroxylase that has been used in some severe cases to achieve a rapid reduction in plasma cortisol levels.[3,10,12]

Combination treatments

The combined use of ketoconazole and metyrapone is a standard practice when the normalization of plasma cortisol has not been achieved with either drug alone. On the other hand, the additive or synergistic effects of the combination allow the same results to be achieved with lower doses, thus minimizing the potential side effects.

The results of the combination of mitotane, metyrapone, and ketoconazole in patients with advanced ACTH-dependent Cushing's syndrome (four with Cushing's disease and seven ectopic) have recently been reported.[13] Significant clinical improvement, with rapid reduction of urinary free cortisol, was seen at 24–48 h of treatment start,

and this effect was maintained during follow-up. In seven patients ketoconazole and metyrapone was discontinued at 3.5 months, and urinary free cortisol levels continued to be controlled on mitotane alone. Surgery was performed in five patients, who achieved postoperative remission. Four of the patients recovered adrenal function after mitotane discontinuation. The most common side effects included gastrointestinal effects, hypokalemia, and significant LDL-C and GGT increases. Liver toxicity led to ketoconazole discontinuation in one patient. Thus, when immediate etiological treatment is not possible in ACTH-dependent Cushing's syndrome due to disease severity, combined treatment with mitotane, metyrapone, and ketoconazole may be an effective alternative to bilateral adrenalectomy.

Drugs with central action on ACTH secretion

In recent years, research on the medical treatment of Cushing's disease has mainly focused on the search for drugs with a direct action on ACTH secretion.

Somatostatin analogs. Pasireotide

ACTH-secreting pituitary adenomas express somatostatin receptors, mainly subtype 5 receptors, but also subtype 1 and 2 receptors.[14,15] Activation of subtype 5 inhibits ACTH secretion.

The currently available somatostatin analogs, octreotide and lanreotide, show a high affinity for subtype sst2 and a marginal affinity for subtype 5. This explains, at least partly, their lack of effectiveness for the treatment of Cushing's disease.

Pasireotide is a new investigational somatostatin analog with a multi-receptor action, showing a high affinity for subtypes sst1, 2, and 5. As compared to octreotide, pasireotide has 40-, 30-, and 5-fold greater *in vitro* affinities for sst5, 1, and 3 receptors respectively, and a two-fold greater affinity for sst2.[16] Because of these differences in affinity, pasireotide may be expected to have a greater inhibitory effect of hormone secretion as compared to octreotide in cells that express somatostatin receptor subtypes other than sst2.

In vitro preclinical studies with somatostatin analogs

In cultures of rat corticotroph cells, treatment with native somatostatin is unable to decrease ACTH secretion. However, reduced secretion occurs when culture is performed in a glucocorticoid-free medium. Thus, the presence of glucocorticoids appears to decrease the inhibitory effect of somatostatin on ACTH secretion through downregulation of the somatostatin binding sites.[17]

In vitro studies on ACTH-secreting pituitary adenomas and on a cell line of murine corticotroph tumor (atT-20) show that pasireotide inhibits both basal and CRH-stimulated ACTH release and that this effect is not affected by dexamethasone pretreatment. By contrast, the inhibitory effect of octreotide, in addition to being lower, was almost completely blocked when prior treatment was administered with dexamethasone.[18] All the foregoing suggests that sst2 may be downregulated by glucocorticoids, including endogenous

hypercortisolism, and that sst5 is more resistant to down-regulation induced by glucocorticoids.

Thus, the greater efficacy on ACTH release of sst5 agonists as compared to preferential sst2 agonists could depend on the reduction of sst2 expression induced by glucocorticoids. This also suggests that inhibition of ACTH release and, thus, of cortisol through sst5 may restore sst2 expression, which would result in pasireotide having a greater effect.[19]

Studies in human ACTH-secreting pituitary adenomas suggest pasireotide has an effect not only on secretion, but also on proliferation, although in some adenomas, such as in acromegaly, these effects may be dissociated.[20]

Clinical efficacy studies

Clinical studies conducted with octreotide and lanreotide have shown their lack of efficacy. However, some studies have found that octreotide may decrease ACTH secretion in Nelson's syndrome. This may be explained by the lack of sst2 downregulation induced by glucocorticoids.[10]

The results of a phase 3 multicenter study with pasireotide have recently been reported.[21] Patients with Cushing's disease having urinary free cortisol levels at least 1.5 times higher than the upper normal limit who were not amenable to surgery, had not been given radiation therapy during the preceding 10 years, and who had no campimetric changes due to chiasmatic compression, symptomatic cholelithiasis, or glycosylated hemoglobin values higher than 8% were selected for the study. A total of 162 patients were randomized. Of these, 82 patients were assigned to receive 600 μg, and 80 to receive 900 μg twice daily by the subcutaneous route. At month 3, patients who had urinary free cortisol levels not exceeding twice the upper normal limit and who did not exceed their basal value continued on the same dose, while the dosage of all the other patients was additionally increased by 300 μg twice daily. This treatment was continued until month 6. From month 6 to month 12 there was an open-label phase where the dosage could be increased up to 1200 μg twice daily if urinary free cortisol levels were above the upper reference limit.

Urinary free cortisol levels normalized in approximately 20% of patients (12 of the 82 patients assigned to the 600 μg group and 21 of the 80 patients assigned to the 900 μg group). Normalization was most frequently achieved in patients with basal levels not exceeding five times the upper normal limit. Mean urinary free cortisol reduction was approximately 50% at month 2, and remained stable in both groups. In addition, overall decreases were achieved in serum and salivary cortisol levels and ACTH levels. Clinical effects included weight and blood pressure[22] reduction and improvement in quality of life tests.[23]

Safety and tolerability

In this study, rates of gastrointestinal side effects (diarrhea 58%, nausea 52%, abdominal pain 24%) and cholelithiasis (30%) were similar to those seen with other somatostatin analogs.

However, a greater frequency of occurrence or worsening of hyperglycemia was found, despite a reduction in cortisol secretion. In studies conducted in healthy volunteers, pasireotide decreased insulin and incretin (GLP-1 and GIP) secretion, while insulin sensitivity was apparently not affected.[24] In a phase 2 study in Cushing's disease, hyperglycemia was found in 36% of patients. Suppression of insulin secretion was shown, but had no significant effect on glucagon secretion.[25]

In the abovementioned phase 3 study, blood glucose and glycosylated hemoglobin levels increased soon after the start of treatment and remained more or less stable for the rest of the study. Mean basal hemoglobin was 5.8% and increased to 7.2% and 7.4% in the groups treated with 600 and 900 μg, respectively. Among those patients who had no diabetes mellitus before study start, 48% had glycosylated hemoglobin values of 6.5% or higher at study end. Of the 129 patients who did not receive antidiabetic treatment before study entry, 53 (41%) required the start of at least one antidiabetic drug during the study, and 21 out of 33 patients (64%) who were receiving antidiabetic medication before study start required additional treatment. No decompensation occurred as ketoacidosis or hyperosmolar state.

A recently reported 24-month extension of this study found no worsening or increase in the proportion of patients with hyperglycemia.[26]

An interesting finding of this study was that both treatment response and hyperglycemia occurred a few weeks after study start and remained stable over time. Consequently, the decision as to whether or not the study should be continued or other drugs should be added could be taken a few weeks after study start based on efficacy or adverse effects.

Dopamine agonists. Cabergoline

Dopamine is a catecholamine with various physiological properties, in particular neurotransmission and hormone secretion control. Dopamine receptors (DRs) belong to the family of G protein-coupled membrane receptors. There are five subtypes (D1–D5) of DRs, divided into D1-like (D1, D5) and D2-like (D2–D4) groups. D1 receptors have a stimulating effect, while D2 receptors are usually associated with an inhibitory action.[27]

DRs are distributed in many tissues. There are no conclusive data showing that ACTH secretion is directly regulated by dopamine receptors in normal human corticotroph cells.[28] However, it is known that the intermediate pituitary lobe of rats is under inhibitory control by hypothalamic dopaminergic neurons. In humans, the intermediate lobe is a rudimentary structure, but appears to have some biological functions.[29] Corticotroph adenomas originating here may have a greater response to dopaminergic drugs.[28]

DR2 receptors have been found in up to 80% of human corticotroph pituitary adenomas, and their presence shows a good correlation to ACTH secretion. In *in vitro* corticotroph adenomas with high DR2 expression, acute inhibition rates of ACTH release by 43% and 60% were seen with bromocriptine and cabergoline respectively. By contrast, adenomas not expressing DR2 did not respond to dopamine agonists.[30]

Clinical efficacy studies

Early studies with dopamine agonists in Cushing's disease were conducted with bromocriptine. Decreased ACTH secretion was seen in almost 50% of patients, but only a minority had a sustained response.[10]

Cabergoline was expected to achieve better results because of its greater ability to bind to D2 receptors and its longer half-life.

A short-term study (three months) in 20 patients with Cushing's disease who were treated with a weekly dose of 3 mg showed a significant decrease in urinary free cortisol levels in 60% of patients, of whom 40% achieved normalization.[30] An extension of this study[31] showed that cabergoline, administered for 24 months at a dose ranging from 1 to 7 mg weekly, maintained control of cortisol secretion in 40% of cases. Blood pressure and glucose tolerance improvements were also achieved in most patients.

Additional series with smaller patient samples have been reported. In one of these, including 12 patients treated for six months with a dose of 2–3 mg weekly, normalization of urinary free cortisol levels was achieved in three patients.[32] In another series in which eight patients were administered doses of 0.75–3 mg weekly for 20–28 weeks, urinary free cortisol levels normalized in 38% of patients and decreased in an additional 38%.[27]

Safety and tolerability

Cabergoline is a drug that has been used for years for other indications, and ample information is therefore available about its tolerability. The most controversial issue is its long-term effect on cardiac valves, particularly when used at higher doses, such as in Parkinson's disease. The fact that higher doses than those used in prolactinoma are usually required in Cushing's disease raises some uncertainty about the potential long-term cardiac side effects.[10]

No severe side effects were seen in the abovementioned larger series.[31] Only two cases of high blood pressure associated with severe asthenia that required treatment discontinuation at 12 and 18 months were reported. Transient asthenia and instability that did not require drug discontinuation were also reported.

Combinations with somatostatin analogs and dopamine agonists

Because of the presence of DR and sst receptors in human corticotroph adenomas, combined treatment with dopamine agonists and somatostatin analogs such as cabergoline and pasireotide appears logical, and chimeric drugs such as dopastatin (BIM-23A760) may possibly be used in the future.

Feelders et al.[33] conducted an 80-day study where pasireotide was initially administered as monotherapy and cabergoline and low dose ketoconazole were sequentially added at 4 and 8 weeks respectively, as normalization of urinary cortisol levels was achieved. This approach achieved normalization in 90% of patients. Pasireotide monotherapy normalized urinary free cortisol in 5 out of 17 patients (29%). Cabergoline addition resulted in normalization in another four patients (24%), and all other patients, except one, experienced a mean 48% reduction in urinary cortisol levels. The addition of ketoconazole resulted in normalization of urinary cortisol in six additional patients (35%).

In another study, the addition of ketoconazole to cabergoline also increased the proportion of patients who achieved normalization of urinary cortisol.[32]

Thus, a combination of drugs with additive or enhancing effects appears to be a reasonable approach for achieving greater efficacy and making possible a decrease in dosage and adverse effects.

Retinoic acid

Retinoic acid has been used to treat various types of cancer. Its antiproliferative and ACTH inhibitory effects have been demonstrated both *in vitro* and in experimental animals. The efficacy of retinoic acid in Cushing's disease needs to be confirmed in clinical trials.[34]

PPAR-γ receptor agonists

The identification of PPAR-γ nuclear receptors in ACTH-secreting pituitary tumors in both mice and humans and the observation that treatment with rosiglitazone, a PPAR-γ agonist, had an antiproliferative effect and an effect on ACTH secretion in these tumors suggested the benefits of using glitazones in Cushing's disease.[35]

Some clinical studies with small numbers of patients providing conflicting results have been reported. Two such studies with rosiglitazone in Cushing's disease showed cortisol and ACTH reduction in a proportion of patients. In one study, the use of rosiglitazone 8–16 mg/day in 14 patients achieved cortisol and ACTH reduction and normalization of urinary free cortisol in six patients after 30–60 days of treatment, but no response was seen in any of the other patients.[36] In another study where 10 patients were given doses ranging from 4 to 16 mg for periods ranging from 1 to 8 months, responses were seen in four patients, but normalization was achieved in only one patient.[37] By contrast, no improvement was seen in cortisol and ACTH in a rosiglitazone study where five patients received 45 mg for 30 days.[38]

Glucocorticoid receptor antagonists

Mifepristone (RU-486)

Mifepristone is the only glucocorticoid receptor antagonist available. It achieves rapid improvement in signs and symptoms of hypercortisolism. The main disadvantage of mifepristone is that it increases ACTH and cortisol by reducing negative feedback, and these parameters are therefore not useful for assessing its efficacy. In addition, it promotes the occurrence of hypokalemia because it does not block mineralocorticoid activity.

There are a few reports of the use of mifepristone in Cushing's disease after the failure of other treatments.[39–41] It is mainly indicated when there is a lack of efficacy or intolerance of other treatments, particularly in patients with psychiatric symptoms secondary to hypercortisolism.[42]

The results of a multicenter US study using mifepristone for 24 weeks after the failure of other treatment modalities in 50 patients with Cushing's syndrome (43 ACTH-secreting pituitary adenomas) were recently reported. Patients with type 2 diabetes mellitus/glucose intolerance (29) or high blood pressure (21) were enrolled into the study. Improvements were seen in basal blood glucose and glycosylated

hemoglobin (mean reduction from 7.4 to 6.3). In the group with high blood pressure, diastolic blood pressure reduction was seen in 38% of patients. A significant overall weight reduction was seen, and 87% of patients experienced global clinical improvement. The most common adverse effects were fatigue, nausea, headache, hypokalemia, joint pain, vomiting, edema, and endometrial thickening in women.[43]

Conclusion

Because of the high morbidity and mortality caused by hypercortisolism, effective drugs to control the disease when surgery is not curative should be available. The currently available drugs with an action on adrenal steroidogenesis are highly useful, but loss of efficacy or side effects often cause problems regarding their long-term use. Novel centrally acting drugs currently being tested may possibly allow for improved long-term use, but still appear to be less than ideal. Increased understanding of the biological and molecular characteristics of these tumors, and the characterization of each individual tumor, should allow for the development of more selective drugs in the future.

Conflicts of interest

The authors state that they have no conflicts of interest.

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