

## New options for the medical treatment of Cushing's syndrome

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### ABSTRACT

A number of drugs have been advocated for the medical management of Cushing's syndrome but few have gained widespread acceptance. The most reliably effective agents are metyrapone and ketoconazole as monotherapy, or in combination. Cabergoline may be of value in a minority of patients but pasireotide is a more reliable and effective agent that lowers cortisol secretion in the great majority of patients, although only normalises UFC in a minority. The potential for combination of an agent that blocks adrenal steroidogenesis with inhibition of ACTH secretion by pasireotide needs to be explored.

**Key words:** Cushing's syndrome, medical treatment, dopamine agonists

### INTRODUCTION

The recent licensing in Europe of the somatostatin analog pasireotide for the treatment of Cushing's syndrome must be welcomed because the choice of agents for several decades has been limited to drugs marketed for other purposes used off-license. This review considers the place of pasireotide in the context of other options for the medical therapy of Cushing's syndrome.

Tumor-directed surgery is first-line treatment for virtually all patients with Cushing's syndrome whether it is caused by a pituitary adenoma, an ectopic adrenocorticotrophic hormone (ACTH)-secreting neuroendocrine tumor, or adrenal neoplasm. In patients with ACTH-dependent Cushing's syndrome, laparoscopic bilateral adrenalectomy offers, when performed by an experienced surgeon, a safe and effective means of curing the hypercortisolemia.

The indications for medical therapy to control hypercortisolism are as follows:

- In preparation for surgery in the belief that normalizing circulating cortisol reduces peri-operative morbidity and mortality.
- When doubt persists after initial investigation about the source of ACTH secretion, treatment can be withdrawn after a suitable interval and the patient can be re-investigated.
- After unsuccessful surgery, while considering further surgery such as bilateral adrenalectomy.
- To reduce morbidity in patients with inoperative metastatic adrenocortical carcinoma.
- While waiting for pituitary radiotherapy to be effective, this may be several years.
- If the psychiatric complications of hypercortisolemia are an immediate threat to the patient's safety.

### MONITORING OF DISEASE ACTIVITY

A 24-h urinary free cortisol (UFC) measurement is the most common means of monitoring disease activity, but has a variety of significant limitations. It relies on a complete collection and, not surprisingly, this is often not the case and results in under estimation of disease severity. A risk of effective medical treatment is overtreatment inducing hypoadrenalism, which will go unrecognized

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with UFC measurement. Exclusive reliance on UFC is analogous to managing a diabetic patient by HbA1c without monitoring glucose, which may be acceptable in patients on diet or metformin but unsatisfactory with insulin therapy.

Although more labor intensive measurement of serum cortisol is a more appropriate means of assessing disease activity. The best validated technique is calculation of a mean serum cortisol from multiple measurements during a single day. Studies comparing isotopically calculated cortisol production rates to serum levels indicate that a mean serum cortisol in the range 150-300 nmol/l equates to a normal cortisol production rate, and this should be the target of medical therapy.

Improvement in technology indicate that salivary cortisol measurement may be a suitable and more patient-friendly alternative means of assessing cortisol status. Mass spectrometry allows quantification of cortisol in saliva at low levels, which is not possible by immunoassay, and eliminates the problem of cross reactivity (see below); however, further work is required to define the target range for salivary cortisol levels.

## MEDICAL THERAPY

A variety of agents have been proposed for the medical therapy, many of which are only of historical interest, and there is a near absence of controlled studies of any of them. They target either adrenal steroidogenesis, inhibit pituitary ACTH secretion, or antagonize cortisol action [Table 1].

## INHIBITORS OF CORTISOL SYNTHESIS

Currently, these agents are the most consistently effective means of controlling cortisol secretion.

### METYRAPONE

Metyrapone is a potent, short-acting inhibitor of cortisol

synthesis with a rapid onset of action that acts primarily on the final step in cortisol synthesis, namely the conversion of 11-deoxycortisol to cortisol. The routine starting dose is 250 mg, three times per day, with cortisol levels falling within 2 h of initiating the treatment.<sup>[1]</sup> Serum cortisol levels should be reassessed at 72 h and the dose titrated to achieve a mean cortisol level of 150-300 nmol/l, which may require up to 8 g/day in 3-4 divided doses. Most patients tolerate the drug without difficulty as long as hypoadrenalism is avoided. Nausea, anorexia, and abdominal pain can occur, but usually this is a sign of over-treatment. Metyrapone therapy results in elevated levels of circulating 11-deoxycortisol levels, which can cross-react in serum and urine cortisol immunoassays to result in a failure to appreciate over-treatment and hypoadrenalism.<sup>[2]</sup>

The major limitation of metyrapone is hirsutism and acne in women due to the androgenic effect of cortisol precursors.

### KETOCONAZOLE

Ketoconazole is an imidazole derivative developed as an oral antifungal agent that inhibits cholesterol, sex steroid, and cortisol synthesis.<sup>[3]</sup> It is the most frequently used agent in the treatment of Cushing's syndrome with the starting dose being 200 mg, twice daily, increasing as necessary to 1200 mg/day in four divided doses. In contrast to metyrapone, it can take several weeks to see the full benefit of a dose adjustment, but the risk of hypoadrenalism is less. With time, it is effective at controlling the symptoms of Cushing's syndrome. In women, its antiandrogenic properties are a virtue, but, in men, gynecomastia and reduced libido have been reported. The most common side effects are gastrointestinal upset and skin rashes, but liver enzyme dysfunction can occur in up to 10% of cases, which rarely has proceeded to acute liver failure and fatality. Ketoconazole has the added benefit of reducing the total cholesterol and low-density lipoprotein (LDL) cholesterol.

### MITOTANE

Mitotane is a cytotoxic agent used for the treatment of adrenocortical carcinoma, but it is also of value in controlling hypercortisolemia in benign causes of Cushing's syndrome. Mitotane reduces cortisol production by blocking cholesterol side-chain cleavage and 11  $\beta$ -hydroxylase. The onset of mitotane action is slow with sustained action maintained for several months after discontinuation. When used to inhibit cortisol secretion, mitotane is initiated at a dose of 0.5-1 g/per day, which is titrated against serum cortisol levels by 0.5-1 g every few weeks. Adverse effects such as nausea, anorexia, and diarrhea are common with doses of 2 g/per day and almost universal at doses >4 g/per day. Adrenal

**Table 1: Medical options for the management of Cushing's syndrome**

Glucocorticoid receptor antagonist
RU486 (mifepristone)
Adrenal-directed
metyrapone
ketoconazole
mitotane
trilostane
etomidate
Pituitary-directed
rosiglitazone
dopamine agonists
pasireotide

insufficiency and neurological side effects including abnormal gait, dizziness, vertigo, confusion, and problem of language expression are often seen at higher dose. Abnormal liver enzymes, hypercholesterolemia, skin rash, hypouricemia, gynecomastia in males, and prolonged bleeding time are also well recognized. Changes in hormone binding globulins may result in total hormone measurement being unreliable during treatment and thus caution is required when interpreting serum cortisol levels. Mitotane may induce spontaneous abortion and is a teratogen. Ketoconazole and metyrapone are more effective and better tolerated agents and, therefore, the use of mitotane should be confined to resistant patients.

## ETOMIDATE

Etomidate is a parenteral anesthetic agent that induces hypoadrenalism as it inhibits cortisol synthesis. This unwanted "side-effect" has been utilized at low dose (2.5 mg/h) to correct hypercortisolemia in seriously ill patients with ectopic ACTH production.<sup>[4]</sup> Etomidate's use is limited by the need to be given intravenously, but it has a place in acutely sick patients unable to be treated orally where rapid correction of hypercortisolemia may be life saving.

## AGENTS BLOCKING CORTISOL ACTION

Mifepristone is a potent antagonist of the glucocorticoid and progesterone receptors that blocks cortisol action. Negative feedback at the hypothalamic-pituitary-axis induces increased ACTH and, consequently, cortisol secretion and therefore cortisol cannot be used as a marker of disease activity. Mifepristone, at doses of up to 20 mg/kg, has been successfully used to treat a small number of patients with ectopic ACTH syndrome and there is every reason to believe that it could be successfully used in all patients if it were not for the problem of monitoring therapy, and, until a reporter downstream of the receptor is identified, it is unlikely ever to achieve wide-spread acceptance.

## PITUITARY DIRECTED TREATMENT

Pituitary ACTH secretion is regulated by a number of neurotransmitters including catecholamines, serotonin, acetylcholine,  $\gamma$ -aminobutyric acid (GABA), and peptides. In Cushing's disease, the pituitary tumor remains partially responsive to hypothalamic stimuli, illustrated by responsiveness to exogenous corticotropin-releasing hormone (CRH) and dexamethasone. Reports exist advocating the virtues of various agents, but, until date, none have gained widespread acceptance. However, recent data have renewed interest in the possibility of treating Cushing's disease with

centrally acting drugs that modulate ACTH secretion through dopamine, somatostatin, and PPAR- $\gamma$  receptors.

## DOPAMINE AGONISTS

Bromocriptine and cabergoline are dopamine agonists that have been widely used in the treatment of hyperprolactinaemia and acromegaly. A single dose of bromocriptine caused a fall in ACTH in half of the patients with Cushing's disease, but unfortunately this effect was not maintained in the long term. There are reports that suggest that high-dose bromocriptine (40 mg/day) may result in clinical improvement in up to 50% of patients, but others have found response rate of only 1-2% in the long term. Potential side-effects of bromocriptine include nasal congestion, nausea, postural hypotension, headaches, and hallucination.

The use of cabergoline in the management of Cushing's disease has been more encouraging. In an open-labeled, uncontrolled study, Pivonella *et al.*, found that, in 20 patients with Cushing's disease, cabergoline at doses of up to 7 mg/week for 3 months normalized UFC in 7 (35%) patients, with a further 8 (40%) patients having some response. After 24 months, 8 of the 20 patients remained fully controlled on cabergoline treatment with a median dose of cabergoline 3.5 mg/week. The experience of others is less encouraging and there is a concern about the risk of cabergoline-induced cardiac valve fibrosis.

## PROLIFERATOR-ACTIVATED RECEPTOR- $\gamma$ RECEPTOR AGONISTS

In 2002, the nuclear hormone receptor, peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) was identified on ACTH-secreting pituitary tumors. Mice inoculated with corticotroph At T20 tumor cells treated with the PPAR- $\gamma$  agonist rosiglitazone (150 mg/kg/day) did not develop tumors. However, studies with rosiglitazone in patients with Cushing's disease failed to reproduce the success seen in the laboratory, possibly because of the 1000-fold difference in dose; PPAR- $\gamma$  agonists is not advocated for the treatment of Cushing's syndrome.

## SOMATOSTATIN ANALOGS

There are five subtypes of somatostatin receptors, with sub-type five being predominate on corticotrophomas with activation inhibiting ACTH secretion. There have been occasional reports of successful treatment of Cushing's disease with octreotide and lanreotide, but neither has been consistently effective, probably in part for relatively

low affinity of the analogs for the sub-type five receptor. Pasireotide is a novel somatostatin analog with high affinity for receptor subtypes 1, 2, 3, and particularly 5. An initial study of subcutaneous pasireotide, 600 µg twice daily for 15 days in 39 patients with Cushing's disease documented a fall in 24-h UFC in 76% of patients with normalization of UFC being seen in 17%.<sup>[5]</sup> The data from this study provided the "proof of concept" to justify a larger study. The 12-month, randomized, phase 3, double-blinded study included 162 patients with Cushing's disease in whom baseline UFC was at least 1.5-times the upper limit of the reference range. Patients were randomized to receive 600 or 900 µg, twice daily, subcutaneously for 3 months in the first instance. If, at 3 months, UFC was twice the upper limit of the reference range, the dose was increased by 300 µg twice daily; other patients remained blinded on their initial dose of pasireotide for the duration of the study. The primary endpoint of the study was the rate of the normalization of UFC at 6 months. Median UFC fell by 50% with the benefit being sustained for the 12-month duration of the study. UFC normalized in 15% of patients on 600 µg/day and in 26% of patients on 1200 µg/day. There was a relationship between pre-treatment disease severity and the rate of UFC normalization; 50% of patients treated with 1200 µg/day in whom baseline UFC was less than twice normal, while patients treated with the same dose in whom baseline UFC was 5-times normal had a normalization rate of only 7%. In general, the side effects were similar to those seen with octreotide and lanreotide, with the exception of the high rate of hyperglycemia. Pasireotide was associated with hyperglycemia-related adverse events in 118 of 162 patients, with 74 of the requiring hypoglycemic medication that must be a concern for long-term therapy.<sup>[6]</sup>

## SUMMARY

A number of drugs have been advocated for the medical

management of Cushing's syndrome, but only few have gained widespread acceptance. The most reliably effective agents are metyrapone and ketoconazole as monotherapy or in combination. Cabergoline may be of value in a minority of patients, but pasireotide is a more reliable and effective agent that lowers cortisol secretion in the greater majority of patients, although it only normalizes UFC in a minority. The potential for combination of an agent that blocks adrenal steroidogenesis with inhibition of ACTH secretion by pasireotide needs to be explored.

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