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PLENARY LECTURES

Medical treatment of Cushing's syndrome

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Cushing's syndrome (CS) comprises a large group of signs and symptoms that reflect prolonged and inappropriately high exposure of tissue to glucocorticoids (1). The most common cause is the iatrogenic form. Endogenous CS is a rare disease (the incidence is estimated of 2–3 cases per 1 million inhabitants per year). Excess cortisol production may be caused by either ACTH secretion (from a pituitary or other ectopic tumour) – ACTH-dependant CS or independent adrenal overproduction – ACTH-independent CS. The ACTH-dependant CS is more frequent (80% of cases).

CS is a heterogeneous disorder and requires a multidisciplinary and individualized approach to patient management. As CS is caused by a tumour (pituitary, adrenal or ectopic), producing either ACTH or cortisol, the most common way of treatment is the surgical resection of the tumour, performed by an experienced surgeon, although this is not always possible. Second-line treatments include more radical surgery, radiation therapy (for Cushing's disease), medical therapy, and bilateral adrenalectomy. Because of the significant morbidity of Cushing's syndrome, early diagnosis and prompt therapy are warranted.

The medical therapy of CS may be adrenal-directed and tumour-directed (2).

Adrenal-directed therapy: steroidogenesis inhibitors Adrenal-directed therapy (steroidogenesis inhibitors) may be highly effective but does not treat the underlying tumour or restore normal HPA secretory dynamics. Most experience with steroidogenesis inhibitors has been acquired with ketoconazole and metyrapone, which appear to be more effective and better tolerated than aminoglutethimide (3–12).

Ketoconazole was initially used as antifungal drug. Besides this action, it was proven to inhibit the steroidogenesis at several levels: 20, 22 desmolase (CYP11A1), 11- β -hydroxylase (CYP11B1), and 17, 20 lyase (CYP17). The usual doses are 200 mg twice daily to 400 mg three times daily (total daily dose of 1200 mg)(2). Mild elevations in liver enzymes (up to 3-fold normal), which are transient, are not a contraindication to medical therapy with ketoconazole, but liver function should be monitored carefully because of the rare complication of liver failure. The possibility of the development of hypogonadism in men during ketoconazole therapy may favour the initial use of metyrapone in this population. Conversely, the association of hirsutism with metyrapone treatment in women may make ketoconazole a better choice in this population. Interestingly, in contrast to subjects with an intact HPA axis, patients with pituitary-dependent Cushing's disease show no compensatory rise, or decrease, in ACTH levels upon prolonged administration of ketoconazole. According to human and animal studies, however, this phenomenon does not seem to involve a direct effect on ACTH secretion but rather an adjustment in the sensitivity of the HPA axis (4, 5, 9, 10). Moreover, the ACTH response to CRH in patients with Cushing's disease was enhanced or unchanged during ketoconazole treatment compared with the pre-treatment response (4). Taken together, these findings argue against an additional site of inhibition at the pituitary level, although it was suggested by *in vitro* studies of pituitary corticotrophs (13).

Metyrapone acts by blocking the action of CYP11B1. Metyrapone treatment leads to marked inhibition of aldosterone biosynthesis and accumulation of aldosterone precursors with weak mineralocorticoid activity. Electrolyte balance and blood pressure levels vary individually with the degree of aldosterone inhibition and 11-deoxycorticosterone stimulation. Adverse effects due to increased 11-deoxycorticosterone levels (hypokalemia, oedema, and hypertension) are infrequent (12). At present, metyrapone is not commercially available in the United States, but it can be provided for compassionate use by contacting the manufacturer (Novartis) directly. The usual doses of Metyrapone are 250 to 1500 mg four times daily (total daily dose of 6000 mg) (2).

Mitotane (o'p'-DDD) may prove highly effective in the longterm suppression of hypercortisolism in the majority of patients with CS because of its specific adrenolytic action. Its mechanism of action also prevents the risk of escape phenomenon in response to the ACTH rise that occurs in Cushing's disease when plasma cortisol is decreased (15). However, its onset of action is slow (weeks or months), and the

adverse effects associated with mitotane therapy (mainly digestive and neurological) require careful monitoring of drug levels, and it is routinely used in only a few centres.

Aminoglutethimide is an anticonvulsant drug that inhibits the CYP11A1 and the 11- β -hydroxylase CYP11B1. Because of its serious side effects, it is no longer available worldwide.

In situations where rapid control of cortisol levels is required and oral therapy is problematic, i.v. etomidate therapy may be considered (14) (bolus of 0.03 mg/kg i.v. followed by infusion of 0.1 mg/kg/h. the maximal dosage is 0.3 mg/kg/h (2). Etomidate acts by inhibiting the CYP11B1.

Treatment with the glucocorticoid receptor-antagonist mifepristone (RU486) has been reported in fewer than 20 patients with ectopic ACTH secretion, and its use for this indication is currently investigational (16). There is no significant experience reported yet with this agent in patients with Cushing's disease, and assessment of its efficacy in the absence of a biochemical marker is challenging.

Follow-up evaluations should include the examination of clinical features and 24-h urinary free cortisol (UFC) levels, aiming for normalization of both. A few centers use a cortisol day curve with five measurements of serum cortisol over 12 h, with a goal of maintaining the mean level within normal limits. Blood samples are taken at 0900, 1200, 1500, 1800, and 2100 h, and the mean cortisol levels are calculated. Several assessments may be advisable, because control may be variable with cyclical disease.

The choice of UFC assay should be considered carefully, with tandem mass spectrometry considered most specific, and it is important to note that normal ranges vary greatly depending on the assay method. Although salivary cortisol measurements may be an important endpoint in establishing efficacy and restoration of normal cortisol levels, validation data in patients treated for Cushing's disease are needed. Whichever technique is used, the aim is to restore a 24-hour production rate of cortisol within the normal range, although circadian rhythmicity may not necessarily be restored. However, the clinical impact of these abnormal rhythms remains unclear.

Adrenal-directed medical therapy is effective in the majority of patients in a dose-dependent manner. Its indications might include the preoperative preparation of patients to correct severe complications of the disease quickly. In this context, the possibility of avoiding hypoadrenalism immediately after surgery by normalization of cortisol production for a sufficient length of time preoperatively, pertains to clinical observation rather than randomized clinical trials and should be better explored. Drug control of hypercortisolism is also suitable for patients, awaiting a response to radiation therapy and whenever a palliative treatment is needed. In general, definitive therapy, either surgery or radiotherapy should be considered for all patients, and long-term medical therapy alone is rarely indicated.

Tumour-directed medical therapy Pituitary-directed therapy targets the underlying cause of the disease, and therefore, several investigational agents are under evaluation. Despite initial promise, subsequent studies do not support a routine clinical role for the use of peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists, such as rosiglitazone and pioglitazone (17). Although retinoic acid is effective at reducing ACTH in animal models and in dogs with Cushing's disease, the effective dose used is high and human clinical trial results are not currently available. Current medical therapies targeted to the corticotroph tumour itself have not been uniformly successful. However, a medical therapy that acts directly on the pituitary tumour to normalize ACTH secretion and inhibit tumour growth would represent a major non-surgical advance in the treatment of this disease. Molecular studies provide a rationale for the use of somatostatin receptor ligands for the treatment of corticotroph adenomas, because these tumours express somatostatin receptor subtypes sst1, sst2, and sst5, although expression of sst5 predominates (18). The commercially available somatostatin analogs octreotide and lanreotide are predominantly sst2-selective ligands and are mostly ineffective in treating Cushing's disease. Somatostatin analogs with a broader somatostatin receptor-subtype affinity might be more effective. Pasireotide (SOM230; Novartis, Basel, Switzerland), which has high affinity for sst1–3 and especially sst5, shows promise as a tumour-directed medical therapy in patients with Cushing's disease (18). Longer-term trials are needed to determine the safety and efficacy of pasireotide. The dopamine D2 receptor is expressed in more than 75% of corticotroph pituitary adenomas (19). In long-term studies with bromocriptine, disease remission was confirmed in only a small minority of patients. A small, short-term study suggests that cabergoline at dosages of 2–3.5 mg/week may be effective in treating a subset of patients with Cushing's disease (19). However, more data are required not only for efficacy but also to address the long-term safety of cabergoline in these patients. The use of combination pituitary-directed drug therapy (e.g. a dopamine D2

receptor agonist plus a sst receptor ligand) is an exciting concept that has not been evaluated to date. Previous studies have shown that serotonin antagonists and γ -aminobutyric acid (GABA) agonists are generally ineffective and are not routinely recommended.

Treatment strategies The treatment of choice for Cushing's disease (the most frequent cause of CS) is the selective transphenoidal surgery. Medical treatment can be considered before the operation in cases of severe hypercortisolism in order to diminish the morbidity and the mortality, linked to the intervention. The most frequently used drug are Ketoconazole and o'p'-DDD. When surgery is not successful or is contraindicated, o'p'-DDD is prescribed. Because of its slow start of action, Ketoconazole should be administered in the beginning of treatment.

In cases of adrenal adenoma, responsible for CS (ACTH-independent CS), surgery is preferable. Medical treatment (Ketoconazole) can be prescribed in the preoperative period in order to diminish the hypercortisolism and to prepare better the patient for the operation. o'p'-DDD treatment is not advisable in order not to alter the contralateral adrenal gland.

After surgical treatment of adrenal carcinoma, responsible for CS, o'p'-DDD is most often prescribed because of its adrenolytic action with or without Ketoconazole.

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