Therapeutic innovations in endocrine diseases – Part 1: New medical treatments for chronic excess of endogenous cortisol (Cushing’s syndrome)

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Cushing’s syndrome is still a rare condition; yet it has recently become a target for new drugs! Chronic cortisol excess seems to inescapably attract the appetite of many pharmaceutical firms that have suddenly identified a new “unmet medical need”...

Cushing’s disease, due to a pituitary corticotroph tumor, is by far the most frequent cause of Cushing’s syndrome (60–70% of cases); the ectopic ACTH syndrome, due to ACTH secretion by non-pituitary tumors, occurs in less than 10% of cases. Then, primary adrenocortical lesions may cause “pituitary-independent” Cushing’s syndrome in case of unilateral tumors (20–30% of cases), which can be benign or malignant, or in rare cases with bilateral adrenocortical hyperplasias.

There are many ways to fight against chronic endogenous cortisol excess with drugs that depend on the cause of the syndrome, and the mechanism of action of the drug:

- Drugs acting directly at the corticotroph tumor (mainly cabergoline and pasireotide) will be active only in the case of Cushing’s disease. As well as a chemotherapeutic agent as temodal which has recently shown some efficacy in aggressive corticotroph adenomas;
- Drugs acting directly on some non-pituitary tumors (somatostatin- and/or dopaminergic analogs; antimitotic) may be active in some cases of the ectopic ACTH syndrome;
- Theoretically, new molecules that would act as ACTH-antagonists at the MC2 receptor on the normal adrenocortical cells, should be active in all forms of ACTH-dependent Cushing’s syndrome (Cushing’s disease, the ectopic ACTH syndrome, the rare syndrome of primary bilateral adrenocortical hyperplasia where local production of ACTH is believed to exert an autocrine pathophysiological action);

Summary

Diverse hormonal, antisecretory, antitumoural or immunomodulatory therapeutic innovations act for broadening the management scope of adrenal, pituitary and endocrine tumours.
• drugs that directly inhibit cortisol synthesis at the adrenal cortex: inhibitors of steroidogenesis such as metyrapone, ketoconazole, or LCI 699, or adrenalytics such as O,p’DDD would benefit all causes of Cushing’s syndrome, with a special interest of the latter one in adrenocortical carcinomas;
• drugs which oppose the action of cortisol on its receptor (Mifepristone) would be active, as well, in all causes;
• new drugs have recently emerged that create – with older ones – a vast “repertoire” of anticortisolic treatments.

**Targeting the pituitary corticotroph adenoma**

**Cabergoline**

Several studies have reported that this dopamine D2 receptor agonist could normalize urinary cortisol in ca. 30% of Cushing’s disease patients. For unknown reasons, some patients seem to escape after a few months of treatment [1-3]. Except for the usual adverse events common to all dopaminergic drugs, it is a rather well-tolerated treatment.

**Pasireotide**

Pasireotide is a new somatostatin analog (SOM 230, Signifor®, Novartis) which acts preferentially on the type 5 SST receptor, explaining its beneficial action on corticotroph adenomas [4-7]. On this basis, a large multicentric phase III trial demonstrated its action in Cushing’s disease patients given up to 900 μg bid in subcutaneous injection [7]: 50% of the patients showed a definitive decrease in urinary cortisol compared to baseline, although it was eventually normalized in only 25% of the patients. The classical adverse events of somatostatinergic drugs are observed, mainly gastro-intestinal. However, a major drawback of this treatment is a frequent adverse effect causing hyperglycemia events in as many as 75% of the patients, most certainly because the drug also acts as an inhibitor of insulin secretion (see further special article by J.-L. Wémeau) [8].

**Targeting the adrenal cortex**

**Inhibition of adrenal steroidogenesis: ketoconazole and metyrapone**

Cortisol synthesis can be rapidly suppressed with two oral agents that are available worldwide, ketoconazole and metyrapone (the latter under special request in the USA). The two large series, with more than 100 patients each, have recently been reported which show a success rate of ca. 50% for the two drugs. Yet, their retrospective nature brings obvious limitations [9,10]. Lowering cortisol in Cushing’s disease will inevitably trigger an ACTH response by the pituitary adenoma with the risk of escape to treatment efficacy, and an increase of steroid precursors (androgens and mineralocorticoids) under metyrapone. Finally, some adverse effects can be observed: liver injury with ketoconazole, mild GI upset, and dizziness, and excess mineralocorticoid and adrenal androgens due to CYP11B1 blockade with metyrapone with the risk of hypertension, edema, hypokalemia and hirsutism in women.

Ketoconazole is a mixture of two enantiomers; one of them ketoconazole (2S, 4R) might supposedly have less liver adverse effect and is now under phase 3 study in Cushing’s syndrome (Contendo).

These medications are rarely used as long term monotherapy in Cushing’s disease. Rather, they can be used as non-permanent adjuncts, in preparation to pituitary surgery, waiting for full action of radiotherapy, or in special situations where severe hypercortisolism contraindicates immediate surgery and one takes advantage of their rapid onset of action, particularly in combined treatment (see further).

**LCI 699 (osilodrostat)**

This new molecule was originally developed by Novartis as a CYP11B2 inhibitor for the treatment of hypertension. Yet, it was found to also inhibit CYP11B1 and cortisol synthesis. Recent proof of concept studies, in few cases and short period of time, has shown LCI 699 to be highly efficient in normalizing urinary cortisol in patients with Cushing’s disease in more than 80% of the patients [11].

Like metyrapone, LCI 699 induces an ACH rise and increased mineralocorticoids and androgens in women. Yet, it seems more powerful, has a longer plasma half-life, and few adverse events like GI upset or dizziness. Further and longer studies are on-going.

**Etomidate**

Etomidate is an imidazole derivative which blocks the CYP11B1. This anaesthetic drug is given intravenously, and is occasionally used in patients with severe hypercortisolism, and which cannot be treated by oral medications [12].

**Lysodren: a dedicated adrenolytic**

Among anti-adrenocortical drugs, O,p’DDD (Lysodren, HRA-Pharma®) (1-dichloro-2-[0-chlorophenyl]-2-[p-chlorophenyl]-ethane) has a unique adrenolytic action; it specifically destroys the adrenocortical cortex, resulting in a “chemical adrenalectomy”. Patients with Cushing’s syndrome almost invariably reduce their cortisol production on O,p’DDD, in about 80% of cases. Direct indicators of plasma free cortisol, such as salivary or urinary cortisol, are the best parameters to monitor its efficiency. Decreased cortisol production is a slow phenomenon that manifests after 1 or 2 months of treatment.

Although O,p’DDD is a highly effective adrenolytic drug with unique properties, its use as a sole therapeutic means in Cushing’s syndrome has several limitations. Because of its numerous, rather than serious, side effects (gastro-intestinal, altered CNS functions, hypercholesterolemia), its particular kinetics, and its highly variable bioavailability, it necessitates a close and repeated monitoring. Although its efficacy may last for years in a given patient, it is most often only transient.
The largest series of Cushing’s disease patients on long-term treatment with the sole O,p’DDD was recently reported, showing a rate of normalized or suppressed urinary cortisol in 71% of the patients [13].

**Targeting the glucocorticoid receptor**

**Mifepristone**

Mifepristone (RU 486, Korlim), originally developed as an anti-progesterone drug (and presently used in many countries as a contragestive), was also found to be an antiglucocorticoid drug potentially active in man [14].

Until recently, several papers and a review of them had provided evidence that it could be of benefit in occasional cases of Cushing’s syndrome, including patients with Cushing’s disease. The SEISMIC study in USA was the first that included systematically a series of adult patients with various causes of Cushing’s syndrome and type 2 diabetes mellitus or hypertension, among which 42 patients with Cushing’s disease that had failed pituitary surgery [15]. This 24-week, open label, multicenter study administered mifepristone as a single oral dose, between 300- and 1200 mg/day. There was a clear benefit towards some peripheral features due to cortisol action: mean weight dropped 5.7%; there was a significant improvement in glucose metabolism, insulin resistance, cognition, quality of life. Common adverse events were observed, 88% of the patients experienced study-related AEs: fatigue, arthralgia, nausea, vomiting headache, low potassium, edema, and endometrial thickening in women often leading to abnormal vaginal bleeding.

This study shows that this original approach, opposing glucocorticoid action, has indeed some efficacy. This study showed some efficacy of retinoic acid in three of seven Cushing’s disease patients [18].

**Combining drugs**

Recently, two “combined” approaches have further documented this approach, in rather convincing studies, in two contrasted situations.

In patients with Cushing’s disease severe enough to be clear contra-indications to any type of surgery (cardiac failure, recent pulmonary embolism...), a “tritherapy” approach used the simultaneous administration of two steroid inhibitors, acting at different steps of the steroidogenesis, ketoconazole and metyrapone, together with small amounts of O,p’DDD, acting as a slow adrenolytic [16]. This cocktail was higly efficient, inducing normalization of extremely high initial urinary cortisol within a few days! Interestingly, after a few weeks, the steroid inhibitors could often be stopped, at a time when the adrenolytic action of O,p’DDD had been fully efficient, eliminating the risk of escape phenomenon.

In a different setting, patients with classical Cushing’s disease (not severe) were “sequentially” treated with up to three different medications, starting with pasireotide alone first, adding then cabergoline, and finally ketoconazole, as needed. Under this sequential approach, a majority of the patients (15 of 17) were eventually controlled [17].

**Lost ... or future directions?**

The possible use of PPARγ agonists or retinoic acid as inhibitors of ACTH secretion in man has not hold the promises expected from experimental data in vitro or in animal models. Still, a study showed some efficacy of retinoic acid in three of seven Cushing’s disease patients... [18].

New combined therapies can be easily imagined... trials are on-going which combine dopamine- (cabergoline) and SST5- (pasireotide) agonist activities with the idea to synergize their inhibition of ACTH secretion. Drugs that combine the two actions in a single molecule such as dopastatin (a chimeric dopamine/somatostatin agonist from Ipsen) might be candidates.

The antimitotic drug, temozolomide (Temodal®) seems to be effective in a third of aggressive corticotroph macroadenomas [19]; recent elucidation of the pathophysiology of corticotroph tumors have highlighted the role of the E2F/cyclin E pathway [20] and of the EGF receptor which may be overactivated through somatic mutations of USP8 in a third of corticotroph adenomas [21,22]: the first molecular alteration might suggest the use of roscovitine in clinical trials.

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References


