

## Exciting Developments in the Medical Management of Cushing's Disease

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### Abstract

Until recently, there have been few options for the treatment of patients with Cushing's disease who have failed surgery or have recurred. With the approval of US Food and Drug Administration (FDA) and European Medicines Agency (EMA) of mifepristone and pasireotide, endocrinologists now have additional therapies they can consider for their Cushing's disease patients. Each of these medications has its own positive characteristics and adverse effects so that patient-specific characteristics must be taken into account when deciding on a suitable medical therapy.

### Keywords

Cushing's disease, mifepristone, pasireotide

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In 1932, Dr Harvey Cushing published his findings on a series of patients with what he called the "killing disease," revealing that the median survival for most of his patients was less than 5 years from diagnosis.<sup>1</sup> With advances in surgical techniques and medical management of comorbidities, the standardized mortality ratio for patients with Cushing's disease still is elevated two- to fivefold. The surgical remission rates for corticotroph adenomas are approximately 75 % for microadenomas and <50 % for macroadenomas, although this is dependent on the surgical center.<sup>2</sup> Further, recurrence rates are substantial. Endocrinologists have been left with few options for the treatment of patients who have failed surgery or have recurred. Ketoconazole inhibits multiple steps in cortisol synthesis, but has been subject to a black box warning from the US Food and Drug Administration (FDA) regarding potential for liver damage. Off-label use of the dopamine agonist, cabergoline, has been shown to lower cortisol levels, but only in a subset of patients and, even then, some responders will escape from control and manifest elevated cortisol.<sup>3</sup> At the extreme, adrenalectomy is an option but requires that there is good control of the pituitary adenoma, usually by prior treatment with radiotherapy, or there is risk of unchecked growth of the residual tumor cells, resulting in Nelson's disease.

Three years ago, our armoury against Cushing's disease was expanded with the regulatory approval of two pharmaceutical agents. Mifepristone (Korlym, Corcept Therapeutics) (previously known as RU486) is a glucocorticoid receptor antagonist that blocks the effects of cortisol at the tissue level. It was approved by the European Medicines Agency (EMA) in 2011 as an orphan drug for the treatment of endogenous hypercortisolemia. Shortly after, the FDA approved mifepristone for the treatment of hyperglycemia associated

with hypercortisolemia. The second addition was pasireotide (Signifor, Novartis Pharmaceuticals), which is a somatostatin receptor agonist (SRA) approved by the EMA and FDA in 2012. Pasireotide has a strong affinity for somatostatin receptor 5, which enables it to inhibit adrenocorticotrophic hormone (ACTH) secretion from corticotroph adenoma cells, unlike its predecessors octreotide and lanreotide. For Cushing's disease patients who are out of options, both therapies have potential. However, the choice of the right therapy must take into account patient-specific characteristics and the positive features and adverse effects of both drugs.

### Mifepristone

Mifepristone is capable of rapid improvement in the clinical signs and symptoms of hypercortisolemia. The SEISMIC trial included subjects with Cushing's syndrome of many etiologies: adrenocortical carcinoma, ectopic ACTH, bilateral adrenal hyperplasia, and corticotroph adenomas.<sup>4</sup> After 24 weeks of therapy, those subjects with a previous diagnosis of diabetes had improved glucose levels, including lowered fasting glucose, glycated hemoglobin, and glucose excursions during glucose tolerance testing. Thus, the FDA approval was for the treatment of hypercortisolemia accompanied by hyperglycemia. Weight decreased and there were improvements in the scores of questionnaires designed to test for depression, cognition, and quality of life.

As mifepristone blocks cortisol feedback at the level of the corticotroph adenoma, the ACTH and cortisol levels rise two- to threefold,<sup>5</sup> so determining clinical efficacy for dose titration can be challenging, and the clinician has to rely on surrogate markers, such as improvement in Cushing's syndrome-related symptoms and signs as well as indirect

laboratory markers, such as lowered glycated hemoglobin. Mifepristone can be so effective in blocking the glucocorticoid receptor that patients can present with symptoms reminiscent of adrenal insufficiency, including nausea and vomiting, fatigue, arthralgias, and dizziness, in spite of elevated cortisol.<sup>4</sup> It is important that these symptoms are recognized and treated by holding the drug and administering moderate dose of dexamethasone (2–4 mg every 6–12 hours), rather than “weaker” glucocorticoids, in order to overcome the high affinity of mifepristone for the receptor. As mifepristone does not bind and inhibit the mineralocorticoid receptor, the increase in cortisol with therapy can lead to hypokalemia, hypertension, and peripheral edema. These consequences often can be managed with the addition of potassium supplements and spironolactone. Mifepristone also antagonizes the progesterone receptor so that premenopausal women can develop endometrial thickening and dysregulated vaginal bleeding. With the block in feedback on a residual corticotroph adenoma, there is a theoretical concern for unchecked growth, as is seen in Nelson’s syndrome. However, imaging data from the SEISMIC extension revealed that of 36 tumors, only four showed an increase in size and three of these enlarging tumors were invasive macroadenomas at baseline.<sup>5</sup>

Given the above discussion, the choice of mifepristone for a patient with Cushing’s disease must take into patient-specific characteristics. Positive considerations include the need for a fast clinical response, such as for a sick patient who needs to undergo a surgical procedure and patients with hyperglycemia or diabetes secondary to their Cushing’s syndrome. On the other hand, clinicians also must consider the menstrual or reproductive status of their female patients, the ability of the patient to adhere to important medications, such as potassium supplements, as well as the volume and aggressiveness of the residual tumor.

## Pasireotide

Pasireotide is the first approved drug that directly targets the corticotroph adenoma cells and ACTH secretion. It is administered as a subcutaneous injection twice daily. In the phase III study, the median decrease in urine free cortisol (UFC) was more than 60 % at a dose of 900 µg twice per day.<sup>6</sup> Although only one-quarter of patients on the 900 µg dose had normalized UFC at 12 months, baseline data revealed that many of the patients enrolled had “severe” disease at baseline with UFC levels over five times the upper limit of normal. For those with milder disease, in the range of 1.5–2 fold normal, 50 % of patients on 900 µg twice daily had normalized UFC levels.<sup>6</sup> There were improvements in blood pressure, low-density lipoprotein LDL cholesterol, triglycerides, and weight as well as in depression and quality of life scores. Notably, significant decreases in tumor volume (>25 %) were observed in patients from one of the SOM230B2305 study sites: of those with measureable tumor at baseline, eight of eight patients had more than 25 % reduction in tumor volume at 12 months on therapy.<sup>7</sup>

As with other SRAs, gastrointestinal symptoms, such as nausea and diarrhea, can be a factor with pasireotide treatment. One of the most significant adverse effects reported from the phase III trial was that 78 % of patients had a hyperglycemia-related event, including the development of overt diabetes. Data from healthy volunteer studies have revealed that pasireotide has no effect on insulin sensitivity, but insulin secretion is dampened, likely secondary to decreased release of incretin hormones.<sup>8</sup> Congruent with this, an approved glucagon-like peptide-1 receptor agonist and a dipeptidyl peptidase IV inhibitor each had the greatest impact on glucose levels in healthy volunteers who were administered pasireotide.<sup>9</sup>

With phase III trial data in mind, patient-specific characteristics that might weigh favorably for pasireotide treatment include the presence of visible tumor and mild disease. Although pasireotide is costly, a biochemical response to pasireotide is seen within 3 months, so that the clinician can determine if the patient is a responder early into therapy. The patient must be willing to adhere to two injections per day. Also, the glycemic status of the patient at baseline also must be taken into consideration. Patients with preexisting glucose intolerance or diabetes controlled with oral medications may manifest hyperglycemia and have to be monitored frequently on initiation of pasireotide or with an increase in the dose. More data are required to determine the best approach for combating hyperglycemia, but for the time being, there is published guidance from experts who advocate for metformin- and incretin-based therapies as first line, and insulin addition for severe hyperglycemia.<sup>10</sup> For patients already on insulin, and not reliant on incretin or beta-cell insulin secretion, there is potential that treatment of the hypercortisolemia could actually improve insulin resistance, lowering insulin requirements, and these patients also need to be monitored carefully when pasireotide is initiated.

There are other potential therapies on the horizon for Cushing’s syndrome. Like metyrapone, LCI699 is a 11- $\beta$ -hydroxylase (CYP11B1) inhibitor, similar to metyrapone, with mild inhibitory action at aldosterone synthase (CYP11C2). In a recently published dose titration study, LCI699 normalized mean UFC by day 70.<sup>11</sup> COR-003 is a purified enantiomer of ketoconazole that decreases cortisol production through potent inhibition at CYP11B1 and CYP17A1, but may have less hepatotoxic effects with the lower doses needed for inhibition of cortisol synthesis.<sup>12</sup> It will also be valuable to have more data on combination therapies of available and approved medications.

Overall, these new pharmacologic therapies are a welcome addition for endocrinologists and their patients who are suffering with Cushing’s syndrome and disease. Patient-specific characteristics must be taken into account when deciding on an approved medical therapy. Also, we cannot forget that more traditional methods, including repeat surgery, radiotherapy, or even adrenalectomy, may still be the correct approach in the appropriate patient. ■

- Cushing H, The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). 1932, *Obes Res*, 1994;2:486–508.
- Nieman LK, et al., Treatment of Cushing’s syndrome: an endocrine society clinical practice guideline, *J Clin Endocrinol Metab*, 2015;100:2807–31.
- Pivonello R, et al., The medical treatment of Cushing’s disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery, *J Clin Endocrinol Metab*, 2009;94:223–30.
- Fleseriu M, et al., Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing’s syndrome, *J Clin Endocrinol Metab*, 2012;97:2039–49.
- Fleseriu M, et al., Changes in plasma ACTH levels and corticotroph tumor size in patients with Cushing’s disease during long-term treatment with the glucocorticoid receptor antagonist mifepristone, *J Clin Endocrinol Metab*, 2014;99:3718–27.
- Colao A, et al., A 12-month phase 3 study of pasireotide in Cushing’s disease, *N Engl J Med*, 2012;366:914–24.
- Simeoli C, et al., The treatment with pasireotide in Cushing’s disease: effects of long-term treatment on tumor mass in the experience of a single center, *Endocrine*, 2015 [Epub ahead of print].
- Henry RR, et al., Hyperglycemia associated with pasireotide: results from a mechanistic study in healthy volunteers, *J Clin Endocrinol Metab*, 2013;98:3446–53.
- Breitschaft A, et al., Management of hyperglycemia associated with pasireotide (SOM230): healthy volunteer study, *Diabetes Res Clin Pract*, 2014;103:458–65.
- Colao A, et al., Managing hyperglycemia in patients with Cushing’s disease treated with pasireotide: medical expert recommendations, *Pituitary*, 2014;17:180–6.
- Bertagna X, et al., LCI699, a potent 11 $\beta$ -hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing’s disease: results from a multicenter, proof-of-concept study, *J Clin Endocrinol Metab*, 2014;99:1375–83.
- Fleseriu M, Medical treatment of Cushing disease: new targets, new hope, *Endocrinol Metab Clin North Am*, 2015;44:51–70.