PHARMACOTHERAPY

A NEW OPTION FOR CUSHING DISEASE?

Investigators from six centres in Europe and the USA have demonstrated that LCI699, a novel drug blocking a crucial step in cortisol biosynthesis, rapidly normalizes urinary free cortisol levels among patients with Cushing disease.

First characterized as an inhibitor of aldosterone biosynthesis, LCI699 has shown promise for reducing blood pressure among patients with essential hypertension or primary aldosteronism. In addition, LCI699 inhibits the activity of 11 β -hydroxylase (also known as mitochondrial cytochrome P450 11B1), the enzyme required to convert 11-deoxycortisol to cortisol. Given that excess cortisol is a cardinal feature of Cushing disease, LCI699 could offer new hope for managing patients with this condition.

The researchers conducted a proof-of-concept study to assess the efficacy, safety and tolerability of LCI699 among 12 adults with moderate-to-severe Cushing disease. Two equal doses of LCI699 were administered orally each day for 10 weeks, with stepwise dose escalations up to a maximum of 100 mg daily. The primary end point was defined as a fall in urinary free cortisol levels of at least 50% from baseline or a reduction to within the upper limit of the normal range.

All 12 patients achieved the primary end point at least once during treatment, with 11 showing normalized urinary free cortisol levels at the end of the intervention. This response required an LCI699 dose of around 10–20 mg daily and was associated with a concomitant increase in the cortisol precursor 11-deoxycortisol. Mean systolic and diastolic blood pressure both decreased from baseline.

Treatment with LCI699 was generally well-tolerated, with fatigue, nausea and gastrointestinal problems the most frequently reported adverse effects. No drug-related serious adverse events occurred.

Having established the ability of LCI699 to safely and effectively reduce cortisol levels in Cushing disease, the next step for the researchers is to conduct a follow-up trial that enrolls a greater number of patients and pushes the treatment duration beyond 10 weeks.

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Original article Bertagna, X. *et al.* LCI699, a potent 11 β -hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study. *J. Clin. Endocrinol. Metab.* doi:10.1210/jc.2013-2117