



## Cabergoline in Cushing's disease: additional data

Editors

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### INTRODUCTION

Cushing's disease (CD) is a severe endocrine disorder, which may cause several complications and increase mortality rate.

While pituitary surgery remains the standard of care, the possibility of surgical failure and relapse, even after protracted observation, has prompted the search for second-line treatments, including pharmacological ones, which in selected cases may become a first option.

Studies in vitro have shown that the interaction of cabergoline with the dopaminergic D2 receptors expressed by a subset of corticotroph adenomas may lead to inhibition of ACTH secretion.

The role of cabergoline in clinical practice however remains off-label, as the data supporting its use are limited to small studies in the absence of prospective randomized trials.

### THE STUDY

A retrospective study of 62 patients with CD followed between 2003 and 2015 in 13 university hospitals in France and Belgium has been recently published (1). Some of the patients had CD, which persisted or relapsed following pituitary surgery, while others had not previously been treated. Cabergoline was administered as monotherapy in 53 patients, while in 9 it was added to treatment with inhibitors of adrenal steroidogenesis.

### Cabergoline in monotherapy

A complete response, defined as normalization of 24 hours urinary free cortisol (UFC) in two consecutive samples or development of adrenal insufficiency, was observed in 40% of the patients at 12 months. The median dose of cabergoline was 1.5 mg/week (range 0.5-4). Normalization of UFC was associated with improvement of biochemical (morning ACTH, night time cortisol, cortisol day curve) and clinical manifestations of the disease, as measured by a specific clinical score and evaluation of body weight, blood pressure and glycemic control. Over the longer term (19-105 months) biochemical and clinical control of CD was maintained in 23% of patients at a median dose of 1.5 mg/week (range 0.5-3.5), while treatment was discontinued in 28% due to loss of efficacy or intolerance.

### Cabergoline as add-on treatment to ketoconazole or metyrapone

In the course of the first year of treatment a complete response was achieved in 56% of patients at a median dose of 1 mg/week (range 0.5-3.5).

### Observations

Disease control was usually achieved within the first six months of treatment with cabergoline, without a significant correlation between dose of the drug and reduction of UFC. Basal levels of UFC and prolactin were similar among responders and non-responders. The study seems to confirm that cabergoline at a relatively low dose may be effective and well tolerated in a subgroup of patients with CD.

### COMMENTARY

The results of this study support the conclusions of previous prospective and retrospective trials (2-6) and confirm that cabergoline may be effective in a significant minority (20-25%) of patients with CD, both as monotherapy and when added to other treatments.

Despite the limits intrinsic in any retrospective analysis, this study, the largest so far in terms of number of patients evaluated, provides information on biochemical and clinical disease control in the short, medium and long term.

At present, unfortunately, no defined clinical criteria allow to predict response to cabergoline, which is probably related to the expression of D2 receptors by the corticotroph adenoma. A response, however, is usually clinically evident shortly after the treatment is started.

Based on the results of this study, it is possible to propose the following considerations regarding treatment with cabergoline:

- Starting dose of 1.5-2.0 mg/week, whatever the degree of basal hypercortisolism.
- Gradual dose adjustment, based on clinical and biochemical response.
- Response to further treatment unlikely if UFC not significantly reduced after 1-2 months of treatment at the dose of 4 mg/week.
- Need for regular follow up due to the real risk, even after protracted treatment, of adrenal insufficiency or loss of response.

### References

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