Cabergoline for Cushing's disease: a large retrospective multicenter study

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Abstract

Objective: The efficacy of cabergoline in Cushing's disease (CD) is controversial. The aim of this study was to assess the efficacy and tolerability of cabergoline in a large contemporary cohort of patients with CD.

Design: We conducted a retrospective multicenter study from thirteen French and Belgian university hospitals.

Methods: Sixty-two patients with CD received cabergoline monotherapy or add-on therapy. Symptom score, biological markers of hypercortisolism and adverse effects were recorded.

Results: Twenty-one (40%) of 53 patients who received cabergoline monotherapy had normal urinary free cortisol (UFC) values within 12 months (complete responders), and five of these patients developed corticotrophic insufficiency. The fall in UFC was associated with significant reductions in midnight cortisol and plasma ACTH, and with clinical improvement. Compared to other patients, complete responders had similar median baseline UFC (2.0 vs 2.5xULN) and plasma prolactin concentrations but received lower doses of cabergoline (1.5 vs 3.5 mg/week, $P < 0.05$). During long-term treatment (>12 months), cabergoline was withdrawn in 28% of complete responders because of treatment escape or intolerance. Overall, sustained control of hypercortisolism was obtained in 23% of patients for 32.5 months (19–105). Nine patients on steroidogenesis inhibitors received cabergoline add-on therapy for 19 months (1–240). Hypercortisolism was controlled in 56% of these patients during the first year of treatment with cabergoline at 1.0 mg/week (0.5–3.5).

Conclusions: About 20–25% of CD patients are good responders to cabergoline therapy allowing long-term control of hypercortisolism at relatively low dosages and with acceptable tolerability. No single parameter, including the baseline UFC and prolactin levels, predicted the response to cabergoline.

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Introduction

Cushing's disease (CD) is the most common form of Cushing's syndrome and is responsible for numerous comorbidities and increased mortality (1). The recommended first-line treatment for CD is transsphenoidal surgery, which induces remission of hypercortisolism in around 70% of cases. However, CD recurs in ~20% of patients, and the overall cure rate after surgery is therefore about 50% (2). A number of second-line treatments, including pituitary irradiation, bilateral adrenalectomy and drugs, can be offered when surgery is ineffective or not feasible (2). Steroidogenesis inhibitors are the most widely used drugs in this setting. From a pathophysiological standpoint, drugs that target the pituitary adenoma to control ACTH secretion and corticotroph tumor growth would be the ideal alternative treatment (3, 4).

Cabergoline, a dopamine D2 receptor (D2R) agonist, is widely used in the treatment of prolactinomas. D2R is expressed by a subset of corticotroph adenomas and mediates inhibition of ACTH secretion by dopamine agonists *in vitro* (5, 6). In five clinical studies, cabergoline monotherapy normalized 24-h urinary free cortisol (UFC) in 25–40% of CD patients (4, 5, 7, 8, 9). However, these studies were small (maximum 30 patients; <20 patients in 3/5 studies (5, 8, 9)), treatment lasted less than six months in 3/5 studies (5, 8, 9), important biological endpoints such as midnight cortisol were never mentioned and

information on clinical efficacy was lacking in more than half of the studies. The efficacy of cabergoline add-on therapy is also poorly documented. Intriguingly, a recent prospective study failed to show gradual and dose-dependent correction of hypercortisolism at short-term in 20 CD patients treated with increasing doses of cabergoline (0.5–5.0 mg/week) (10). The efficacy of cabergoline in CD is therefore debatable (Table 1).

To improve our knowledge of the efficacy and tolerability of cabergoline in CD patients treated in routine clinical practice, either alone or in combination with steroidogenesis inhibitors, we conducted a large retrospective study.

Patients and methods

An extensive search for CD patients treated with cabergoline was conducted in 13 university hospitals located in France or French-speaking Belgium. Data on 62 CD patients treated with cabergoline between 2003 and 2015 were included in this retrospective analysis, with the following inclusion criteria: (i) active clinical Cushing's disease associated with increased UFC at cabergoline introduction; (ii) the following evidence of CD: identification of an ACTH-immunostaining pituitary adenoma at histological analysis after surgery, or an unequivocal ACTH gradient during IPSS, or an unequivocal pituitary tumor on magnetic resonance

Table 1 Review of literature.

Study	Design	n	Dose (mg/week)	Response criteria	Patients with controlled hypercortisolism (%)	Maximal duration of treatment
Pivonello (2004) (4)	Retrospective, multicenter, monotherapy	10	2.2 (1.0–3.0)	UFC	40	3 months
Pivonello (2009) (6)	Prospective, multicenter, monotherapy	20	3.5 (1.0–7.0)	UFC	35 (short term) 40 (long term)	2 years
Lila (2010) (17)	Prospective, multicenter, monotherapy	20	3.6 (1.0–5.0)	Midnight cortisol and/or LDDST	28	12 months
Godbout (2010) (7)	Retrospective, multicenter, monotherapy	30	2.1 (0.5–4.0)	UFC	37 (short term) 30 (long term)	3 years
Vilar (2010) (8)	Prospective, monocenter, bitherapy	12	2.5 (1.0–3.0)	UFC	25	6 months
Barbot (2014) (9)	Prospective, monocenter, bitherapy	14	2.3 (0.5–3.0)	UFC	33 (short term, monotherapy) 100 (long term, bitherapy)	12 months
Burman (2016) (10)	Prospective, monocenter, monotherapy	20	4.7 (2.5–5.0)	UFC	0	6 weeks

n, number of patients; UFC, urinary free cortisol; LDDST, low-dose dexamethasone suppression test.

imaging (MRI), associated with a positive response to both CRH and high-dose dexamethasone; and (iii) at least one month of cabergoline administration, either alone or as add-on therapy. Patients treated concomitantly with mitotane were excluded.

Previous treatments for CD were recorded, along with the results of clinical, biological and MRI investigations performed before cabergoline introduction and at the last evaluation during treatment.

To evaluate retrospectively the clinical intensity of Cushing's syndrome from medical charts, we developed a clinical score. An arbitrary score of 1 was recorded in the presence of virilism, buffalo hump and obesity. A score of 2 was recorded in the presence of specific or more severe symptoms such as hypokalemia, purple striae, proximal muscle weakness and fragile skin. A score of 1 was recorded for glucose intolerance and a score of 2 for diabetes. Scores of 1 and 2 were recorded for hypertension of grade 1–2 and grade 3 respectively. In the presence of psychiatric disorders, a score of 1 was recorded for sleeping/cognitive disturbances and a score of 2 for severe psychiatric disorders. The maximum score was 17. As some information was missing in medical records, the score of each patient was reported to its theoretical maximum value ([Supplementary Table 1](#), see section on [supplementary data](#) given at the end of this article).

An improvement in body weight was defined as a loss of $\geq 5\%$ ([11](#), [12](#)). An improvement in arterial pressure was defined as a decline in the grade of hypertension ([13](#)), and/or a $\geq 25\%$ reduction in the daily doses of hypotensive drug ([14](#), [15](#)). An improvement in glycemic control was defined as a decrease of $\geq 0.5\%$ in the HbA1c, with no change in antidiabetic treatment, and/or a $\geq 25\%$ reduction in the daily doses of antidiabetic drug ([14](#), [15](#)).

Biological investigations included UFC, 0800-h plasma ACTH, midnight plasma cortisol, the mean of three to six plasma cortisol values (cortisol day curve or CDC) and plasma prolactin and were performed during hospitalization. The cabergoline treatment duration, dosage and tolerability were also recorded.

Adverse effects were classified using the Common Terminology Criteria for Adverse Events (CTCAEv4.02).

The first evaluation after cabergoline prescription was performed within 1 month, 3 months and 6 months in 40, 75 and 100% of patients (median: 2.0 months, range: 0.5–6.0). Once UFC was controlled, UFC was collected with a median frequency of 3.0 months (range: 1.0–6.0). If necessary, the cabergoline dosage was increased by 0.5 to 1.5 mg/week, depending on the investigator's judgment, until the UFC normalized.

Patients whose UFC normalized on two consecutive occasions or who developed corticotrophic insufficiency during treatment were considered to be complete responders. Patients who achieved a $\geq 50\%$ decrease in UFC on two consecutive occasions, without normalization, were considered to be partial responders. An increase in UFC above the normal range during follow-up of complete responders was considered to represent treatment escape. Corticotrophic insufficiency was defined by a 0800-h plasma cortisol < 140 nmol/L and/or a cortisol peak below 500 nmol/L after the short synacthen test.

ACTH and plasma and urinary cortisol were measured by the endocrine reference laboratory in each center, using a variety of assays during the study period, and values were analyzed by comparison with normal ranges used in each assay ([Supplementary Tables 2, 3 and 4](#)).

The data were collected under conditions of regular clinical care. Local ethics committee approval was obtained for the use of the data.

GraphPad Prism, version 6.01–2012 was used for statistical analysis. Most of quantitative data were not normally distributed, and all results are presented as median and range. Median UFC was normalized to the upper normal limit (ULN) of the relevant assay. Quantitative data were compared using Student's *t* test, ANOVA, or the Mann–Whitney, Kruskal–Wallis or Wilcoxon test as appropriate. Qualitative data were analyzed with the χ^2 test or Fisher's exact test as appropriate. Correlation studies were performed using Spearman's test. Statistical significance was set at $P < 0.05$.

Results

The main characteristics of the 62 patients are listed in [Table 2](#).

At baseline, patients had at least one increased UFC and 62% of these had increased UFC in two separate samples. UFC was $1.1\text{--}2 \times \text{ULN}$, $2.1\text{--}4 \times \text{ULN}$ and $> 4 \times \text{ULN}$ in 48%, 32% and 19% of patients respectively.

Cabergoline monotherapy

Fifty-three patients received cabergoline monotherapy. Nine of these patients received cabergoline as first-line therapy, in preparation for pituitary surgery in four cases. Forty-four patients (83%) had persistent or recurrent CD after pituitary surgery. Fifteen patients received conventional ($n=5$) or stereotactic ($n=10$) radiotherapy prior to cabergoline treatment. The median interval

Table 2 Main characteristics of the study population.

Characteristic	Value	n
Age at diagnosis (years)	37.5 (7.0–78.0)	–
Sex ratio (female/male)	50/12	–
Time since diagnosis (years)	7.0 (0–30.0)	–
MRI at diagnosis		–
Microadenoma	48%	
Macroadenoma	32%	
No visible lesion	20%	
Prior pituitary surgery	84%	–
Prior pituitary radiotherapy	26%	–
Comorbidities		
Overweight/obesity	70%	56
Hypertension	60%	58
Diabetes	38%	60
Hypokalemia	7%	60
Baseline laboratory values		
UFC (xULN)	2.1 (1.2–29.4)	62
Midnight plasma cortisol (nmol/L)	372.9 (52–803)	41
CDC (nmol/L)	471.8 (173–969)	54
0800h ACTH (pmol/L)	13.7 (2.9–40.0)	46
Plasma prolactin (ng/mL)	13.0 (1.3–57.4)	30
Prolactin >20 ng/mL	27%	30

n, number of patients with available data; UFC, urinary free cortisol; ULN, upper limit of normal; CDC, cortisol day curve.

between radiotherapy and cabergoline prescription was 2.0 years (range: 0.5–16 years). Eleven patients had previously received steroidogenesis inhibitors that had been withdrawn because of intolerance.

Cabergoline was introduced at various dosages (1.0 mg/week; range: 0.5–6.0). The weekly maintenance

dose of cabergoline was 2.3 mg (range: 0.5–6.0) overall, and <2, 2–3.5 and ≥ 3.5 mg in respectively 41%, 20% and 39% patients. Only two (4%) of the 53 patients received more than 4.0 mg/week. The median treatment duration was seven months (range: 1–105). Eighteen patients (34%) were treated for less than six months, 16 (30%) for between six and 12 months and 19 (36%) for more than 12 months.

During the first year, normal UFC values in at least two consecutive samples were obtained in 21 patients (40%), of whom five (9% of the whole cohort) developed corticotrophic insufficiency. Corticotrophic insufficiency was diagnosed in 5 patients in front of typical clinical symptoms (asthenia and dizziness), low 0800-h plasma cortisol concentrations (36, 99, 108, 135 and 179 nmol/L) and/or associated with low cortisol peak values following the short synacthen test. Corticotrophic insufficiency occurred after three to 105 months of cabergoline exposure at doses ranging from 1.0 to 3.5 mg/week. None of these patients had previously received pituitary radiotherapy. Four of the five patients received hydrocortisone replacement therapy, and cabergoline was withdrawn in the fifth patient. Four patients (7%) were partial responders, whereas 28 patients (53%) had unchanged or increased UFC values (Fig. 1). Importantly, baseline UFC was similar in these three response groups (Table 3). In the complete responders, UFC normalized within three months in 52% of cases and within six

Figure 1

Mains results of cabergoline monotherapy. (A) Changes in urinary free cortisol concentrations before (square) and after (triangle) cabergoline treatment. Stars indicate patients having received pituitary radiotherapy. The gray area indicates the upper limit of normal UFC. Patients are classified according to the cabergoline dosage. (B) Number of complete responders, according to baseline UFC and cabergoline dosage. (C) Time to response in complete responders. UFC, urinary free cortisol; ULN, upper limit of normal; Mo, months.

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Table 3 Main characteristics of complete responders and other patients receiving cabergoline monotherapy.

	Responders (n=21)	Other patients (n=32)	P
Age at diagnosis	45.0 (11–78)	32.5 (7–59)	<0.05
Sex ratio (female/male)	18/3	28/4	1.00
Previous surgery	18 (86%)	26 (81%)	1.00
Previous radiotherapy	7 (33%)	6 (19%)	0.33
Baseline MRI			
Microadenoma	10 (50%)	13 (42%)	0.85
Macroadenoma	6 (30%)	11 (35%)	
No visible lesion	4 (20%)	7 (23%)	
Baseline plasma prolactin (ng/mL)	14.0 (0–43.0); n=15	13.1 (5–57); n=19	0.54
Prolactin ≥ 20 ng/mL	n=3	n=6	
Baseline UFC ($\times$ ULN)	2.0 (1.2–15.8)	2.5 (1.2–29.4)	0.64
Cabergoline dosage (mg/week)	1.5 (0.5–4.0)	3.5 (0.5–6.0)	<0.05
Duration of treatment (month)	28 (3–105)	4 (1–48)	<0.001

n, number of patients with available data; UFC, 24-h urinary free cortisol; ULN, upper limit of normal.

months in 86% of cases. UFC normalized after 12 months in two patients who received low starting doses and a slow dose escalation (Fig. 1).

The cabergoline dosage associated with UFC normalization in complete responders was 1.5 mg/week (range: 0.5–4.0) overall, and <2, 2–3.5 and ≥ 3.5 mg in respectively 52%, 24% and 24% of patients. The maximal dosage used was 4.0 mg/week, in one patient. Interestingly, complete responders received lower doses than other patients at the time cabergoline was discontinued (1.5 mg/week (range: 0.5–4.0) vs 3.5 mg/week (range: 0.5–6.0), $P < 0.05$). No correlation was found between the decrease in UFC and the cabergoline dosage ($r = -0.25$, $P = 0.10$). Among complete responders, the cabergoline dosage associated with UFC control did not differ according to baseline hypercortisolism (mild, moderate or severe, as defined previously; $P = 0.08$) (Fig. 1).

Only age at diagnosis differed between complete responders and the other patients (Table 3). Importantly, baseline prolactin levels were similar.

No significant difference in the prevalence of control of hypercortisolism was found between patients with microadenomas and those with macroadenomas. However, it should be mentioned that four responders (67%) were identified among the six patients with a macroadenoma ≥ 20 mm in size before surgery. This finding is reminiscent of several case reports acknowledging significant shrinkage of corticotrophic macroadenomas with dopamine agonists (16–19).

In complete responders, UFC normalization was associated with a $43 \pm 12\%$ decrease in midnight plasma cortisol (from 331 (range: 250–591) to 180 nmol/L (range: 80–310), $P < 0.01$), and nadir values were below the 200 nmol/L threshold in 50% of patients (20). UFC normalization was also associated with a $54 \pm 9\%$ decrease

in CDCs (from 427 (range: 289–795) to 172 nmol/L (range: 113–374), $P < 0.05$), and a $48 \pm 4\%$ decrease in 0800-h ACTH (from 12.0 (range: 7.7–26.2) to 6.1 pmol/L (range: 3.5–12.0), $P < 0.05$). The decrease in UFC correlated with the decrease in 0800 h plasma ACTH ($r = 0.44$, $P < 0.05$).

The clinical score improved from 31.6 (range: 0–80) to 20.0 (range: 0–40) in complete responders ($P < 0.05$), whereas it was unchanged in the other patients (27.2 (range: 0–74) vs 29.6 (range: 0–61); $P = 0.51$). Specifically, body weight, glycemic control and hypertension improved in respectively 25%, 40% and 33% of complete responders. Hypertension did not improve in patients who were not complete responders.

Eighteen complete responders were treated for more than one year. During long-term follow-up of these patients, a treatment escape occurred in seven patients (39%) after a median treatment duration of 26 months (range: 6–105 months). The increase in UFC was $1.7 \times$ ULN (range: 1.1–2.9) (Fig. 2). An increase in the cabergoline dosage (from 0.5 to 1.0 mg/week and from 1.0 to 2.0 mg/week) yielded secondary normalization of UFC in three patients, whereas treatment was withdrawn in four patients treated with 1.5 to 4.0 mg/week. Treatment was also suspended in a complete responder after diagnosis of grade 2 aortic insufficiency but in whom baseline echocardiography had not been performed prior to cabergoline therapy.

Overall, sustained UFC normalization was obtained for 32.5 months (range: 19–105) in 12 patients (23% of the whole cohort and 67% of complete responders treated for more than a year), at a cabergoline dosage of 1.5 mg/week (range: 0.5–3.5). A sustained improvement in a clinical score was observed during long-term treatment (baseline vs last visit = 25.1 (range: 0–60) vs 20.0 (range: 5–33)).

Figure 2

Long-term response to cabergoline monotherapy. (A) Urinary cortisol level during the long term follow-up in eighteen complete responders treated ≥ 1 year. (B) Focus on the seven patients with treatment escape. Long term complete responders are shown with black lines. Patients who stopped cabergoline because of treatment escape are shown with grey lines. Arrow indicates the increase in cabergoline dosage. The grey area indicates the upper limit of normal of UFC. UFC, urinary free cortisol; ULN, upper limit of normal.

Cabergoline add-on therapy

Nine patients received cabergoline add-on during ongoing treatment with steroidogenesis inhibitors, either in preparation for pituitary surgery (one patient) or after unsuccessful surgery (eight patients). Seven of these nine patients were treated with 600 to 1200 mg/day ketoconazole and two were treated with 3750 to 6000 mg/

day metyrapone, for 18.1 ± 8.2 months. Two patients had received pituitary radiotherapy, less than one year previously.

The maximal weekly dose of cabergoline was 1.0 mg/week overall (range: 0.5–3.5), <2.0 mg in eight patients and 3.5 mg in one patient. The median duration of cabergoline combination therapy was 19 months (range: 1–240). Two of the nine patients were treated for less than five months, one patient was treated for six months and six patients were treated for more than 12 months.

During the first year, five patients (56%) were complete responders and four patients were non-responders (Fig. 3). Baseline UFC was similar in the responders and non-responders (1.8 (range: 1.2–4.0) vs $3.2 \times \text{ULN}$ (range: 1.6–5.6), $P=0.29$). UFC normalized within six months in two patients, and within eight months in three patients.

Responders and non-responders received a similar cabergoline dosage (1.0 mg/week (range: 0.5–3.5) and 1.0 mg/week (range: 0.5–1.5), respectively; $P=0.59$).

In complete responders, UFC normalization was associated with a $57 \pm 26\%$ decrease in midnight cortisol (541 (range: 373–709) to 278 nmol/L (range: 66–489); $P=0.67$), a $47 \pm 18\%$ decrease in CDC (551 (range: 467–635) to 308 nmol/L (range: 164–452), $P=0.33$), and a $38 \pm 32\%$ decrease in 0800h plasma ACTH (23.3 (range: 21.5–25.0) to 14.0 pmol/L (range: 7.7–20.2), $P=0.33$).

Figure 3

Changes in urinary free cortisol concentrations before (square) and after (triangle) cabergoline add-on therapy. Stars indicate patients having received pituitary radiotherapy. The grey area indicates the upper limit of normal UFC. Patients are classified according to the cabergoline dosage. UFC, urinary free cortisol; ULN, upper limit of normal.

The clinical score improved by 10 points in complete responders, whereas it worsened by 6.4 points in non-responders ($P < 0.05$). More specifically, body weight, glycemic control and hypertension improved in respectively 40%, 67% and 50% of complete responders.

Four complete responders to cabergoline add-on therapy were treated for more than one year. A treatment escape occurred in two of these patients, after 12.5 months of treatment (range: 6–19). The increase in UFC was 1.5 and 1.4×ULN. This led to cabergoline withdrawal in one case, while pasireotide add-on induced UFC normalization in the other patient. Treatment was withdrawn for intolerability after 19 months in one patient. Overall, sustained UFC normalization was achieved for 130 months (range: 20–240) in two patients (22% of the add-on subgroup) at a cabergoline dosage of 1.0 mg/week.

Cabergoline tolerability

Safety data were available for 57 patients.

Adverse events occurred in 17 patients (29%): dizziness (14%), nausea (12%), asthenia (12%), dyspepsia (3%), abdominal pain, hypotension, muscle pain, alopecia and edema (2% each). Adverse events were mostly mild (grade 1 or 2). Eight patients (13%) stopped taking cabergoline because of poor tolerance. A grade 4 maniac episode occurred during cabergoline add-on therapy (with ketoconazole) in a patient with a history of depression. The maniac episode subsided after cabergoline withdrawal.

Discussion

This is the largest cohort study of cabergoline therapy in Cushing's disease (4, 5, 7, 8, 9, 10, 21, 22). Interestingly, we identified only 53 cases of cabergoline monotherapy in our nationwide survey spanning a 12-year period, whereas Castinetti *et al.*, using a similar approach, identified more than 200 patients treated with ketoconazole during a 17-year period (23). This suggests that cabergoline has not gained wide acceptance in the treatment of CD.

Our results for cabergoline monotherapy support the efficacy observed in the largest previous series (involving 20 and 30 patients), which showed UFC control in 35% to 37% of patients in the short term, and in 30% to 40% of patients treated for more than 12 months (4, 7).

The relatively modest response rate observed here is not surprising, in view of the low prevalence of high

D2R expression by corticotroph adenomas (5), but it may also be related to the relatively low cabergoline dosage (2.0 mg/week (range: 0.5–6.0)), as most prospective series used maximal median doses of 3.5 and 3.6 mg/week (7, 21). Under-titration occurs frequently in real-life endocrinological treatment of pituitary diseases (23, 24, 25, 26). However, we observed no simple correlation between the cabergoline dosage and the decrease in UFC. Thirty-one patients received at least 2 mg/week of cabergoline in monotherapy. Ten of these patients (32%) were complete responders, four (13%) were partial responders and 17 (55%) were non-responders. Interestingly, our results show that a subset of CD patients is very responsive to D2R agonists and ideal candidates for cabergoline treatment. For example, hypercortisolism was controlled for 6 and 48 months in two patients of our series with only 0.5 mg/week of cabergoline. Such remarkably responsive cases have also been reported by Pivonello *et al.* (7) and Godbout *et al.* (4). In this perspective, we also report for the first time that corticotrophic insufficiency can occur on cabergoline, a phenomenon that may be interpreted as a desirable side effect. Similarly, the probability of controlling hypercortisolism did not correlate with the baseline UFC. More than 67% of complete responders in whom the baseline UFC was above 2×ULN received less than 2.0 mg/week. No single criterion predicted individual response to cabergoline, and the controversial prognostic value of an elevated prolactin concentration (4, 7) was not confirmed here. From a practical perspective, our findings imply that the severity of hypercortisolism should not be a criterion for deciding whether to proceed or not with cabergoline treatment, a concept that is discrepant with the use of cabergoline as an adjunctive treatment for acromegaly associated with mild increase in IGF-1 (27, 28) or with the use of pasireotide in CD (29). Our results also emphasize the need for regular monitoring of morning plasma cortisol, a poor marker of hypercortisolism, to detect corticotrophic insufficiency in controlled patients, including those treated with low doses of cabergoline and because both cabergoline and corticotrophic insufficiency can cause asthenia, dizziness and hypotension. Prospective studies are needed to study the possible correlation between cabergoline efficacy and the intensity of D2R expression in corticotrophic adenomas. This would represent a first step towards individualized medication in this difficult situation.

Our study also provides further insights into the biochemical effects of cabergoline. Although UFC normalization is a relevant therapeutic endpoint, some patients have true hypercortisolism and active disease

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despite normal UFC (29, 30, 31), and lowering the midnight cortisol might be an important goal (32, 33, 34). Although we were unable to study the precise circadian rhythm of plasma cortisol, it is worth mentioning that a 43% decrease in midnight plasma cortisol occurred in complete responders, and that 50% of these patients had nadir values below 200nmol/L. Elsewhere, the average 48% decrease in plasma ACTH in complete responders is consistent with a primary drug action on the corticotrophic adenoma (5, 6).

More data are needed on the clinical impact of cabergoline in CD, especially during long-term treatment. In keeping with our biological findings, UFC normalization was associated with a significant improvement in a clinical score and with sustained regression of cortisol-associated comorbidities during long-term treatment. Contrary to a previous report (7, 35), we observed no improvement in blood pressure in uncontrolled patients; this argues against a beneficial vasodilatory action of cabergoline at the doses used here.

Two specific observations in patients who received cabergoline monotherapy merit discussion. First, the time taken to control UFC was highly variable (<3 months in 52% of patients, <6 months in 86%). Pivonello and Godbout reported a lag time of three months in their series (4, 7). However, prompt control of hypercortisolism is recommended to limit exposure to excess cortisol (36). In contrast, dopamine agonists work quickly in patients with prolactinomas. This slow action of cabergoline would explain the poor results obtained in the short-term prospective study by Burman *et al.* (10), which evaluated the efficacy of increasing cabergoline doses during a period of only six weeks. Elsewhere, the low starting dosage of cabergoline used in our study and in most other published studies, together with the variable timing and intensity of dose increments across the participating centers, prevented us from precisely estimating the time to maximal response. Second, a treatment escape occurred in 39% of complete responders during long-term treatment. This was the case of 19% of 21 patients treated for more than 12 months in others studies (4, 7). Intriguingly, this was observed in a patient who previously experienced corticotrophic insufficiency. The mechanisms responsible for escape to cabergoline treatment are unknown. It may involve receptors downregulation, various post-receptor desensitization mechanisms or selection of adenomatous cells that are less sensitive to D2R agonists. Elsewhere, the possibility of transient fluctuations or poor treatment adherence cannot be excluded. In practical terms, these

observations suggest that repeated clinical and biological evaluation must continue throughout treatment, even when prolonged eucortisolism is obtained. Normal UFC values may be re-established by increasing the cabergoline dosage.

The results of cabergoline add-on during ongoing steroidogenesis inhibition have so far been reported in only 23 patients (8, 9), who were treated for no more than 12 months. Despite the low cabergoline doses used in our study (1.0mg/week (range: 0.5–3.5)), the rate of hypercortisolism control during the first year of treatment compares well with that previously published (63% to 71% of patients controlled on 2.4mg/week) (8, 9). Although very few of our patients received long-term cabergoline add-on therapy, we obtained evidence that efficacy tends to wane, due both to a treatment escape and to late adverse effects. Cabergoline has been reported to help control hypercortisolism when combined with pasireotide and ketoconazole (22).

As previously reported, cabergoline was well tolerated. The withdrawal rate was low, and only one severe psychiatric episode that resolved after drug withdrawal was reported.

The limitations of our study are mostly related to its retrospective design including selection bias and to the lack of a standardized dose escalation plan and monitoring protocol. Within- and between-laboratories variability over time in the methods of cortisol measurement and reference ranges may have induced some random bias in the calculation of CDC and midnight plasma cortisol during the follow-up. In addition, large variations in UFC are common in CD patients (37). Therefore, the differentiation between a definitive control of hypercortisolism secondary to cabergoline treatment and spontaneous normalization of UFC may be difficult in patients with mild hypercortisolism and long intervals between evaluations. Another limitation of our study was the identification of 'true' treatment escapes. Indeed, cabergoline was stopped or increased in dosage when UFC was increased in a single 24-h urine collection. Moreover, the increase in UFC was sometimes minimal ($\leq 1.5 \times \text{ULN}$ in two of the seven patients). It is therefore tempting to speculate that some of these episodes were transient, marginal fluctuations in UFC (37) and that the rate of treatment escape in our study is overestimated. Our assessment of efficacy was hampered by the difficulty of quantifying clinical manifestations from the medical records, and it should be noted that our arbitrary symptom score has not been validated. A standardized tool for evaluating and quantifying clinical manifestations of

Cushing's syndrome is an unmet need. Eight of the 26 complete responders to cabergoline in our study had previously received pituitary radiotherapy, 0.5 to 16 years before cabergoline initiation. Although we cannot exclude a role of pituitary irradiation in the control of hypercortisolism (2, 31, 38), it is noteworthy that none of the patients who developed corticotrophic insufficiency on cabergoline had received radiotherapy. Moreover, the rate of UFC normalization in patients who did not receive radiotherapy within three years before treatment ($n=46$) is 33% for cabergoline monotherapy and 57% for cabergoline add-on therapy. These results are roughly similar to that observed in the whole cohort suggesting that radiotherapy is unlikely to be a confounding factor in this series.

In conclusion, this study conducted in tertiary health care centers suggests that cabergoline provides much the same degree of control of hypercortisolism in Cushing's syndrome as that reported with pituitary-directed medications such as pasireotide (29). Although the efficacy of cabergoline and the time taken to reduce cortisol secretion are less favorable than reported with steroidogenesis inhibitors (23, 24, 39), its simplicity of use, safety profile and relatively low cost make cabergoline a useful drug for a subset of patients who are very responsive to D2R agonists. Unfortunately, there is no simple way of identifying these patients. Some data suggest that the length of exposure to hypercortisolism is somehow related to the persistence of comorbidities and reduced life expectancy in patients cured of Cushing's disease (2, 40). As most of candidates to cabergoline treatment have experienced surgical failure, we anticipate that they may have been exposed to long periods of hypercortisolism and believe that UFC control should be obtained as soon as possible. Complementary studies evaluating precisely the delay in obtaining normalization of UFC in responsive patients are urgently needed (4, 7, 10). In the meantime, we suggest a starting dose of 1.5 to 2.0 mg/week, corresponding to the average dose received by our complete responders and that is usually well tolerated (27, 37). We recommend measuring UFC every 2–4 weeks together with 0800h plasma cortisol during titration and increase cabergoline dosage if UFC is still increased. According to our data and those from the literature, there is probably few chances to control the disease if no significant decrease in UFC is observed after 1–2 months of treatment at 4 mg/week (38). We also recommend regular evaluation of morning plasma cortisol to screen for corticotrophic insufficiency that may be missed by measuring only UFC. Finally, it is important

to watch for signs of therapeutic escape, even in patients with good long-term control.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-0662>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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