CLINICAL STUDY

Cabergoline monotherapy in the long-term treatment of Cushing's disease

Ariane Godbout, Marcos Manavela¹, Karina Danilowicz¹, Hugues Beauregard, Oscar Domingo Bruno¹ and André Lacroix

Endocrinology Division, Department of Medicine, Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Hôtel-Dieu du CHUM, 3840 Rue Saint-Urbain, Montréal, Québec, Canada H2W 1T8 and ¹Endocrinology Division, Hospital de Clinicas, University of Buenos Aires, Buenos Aires 01120 Argentina

(Correspondence should be addressed to A Lacroix; Email: andre.lacroix@umontreal.ca)

Abstract

Background: Cabergoline is a long-acting dopamine receptor agonist used to treat prolactinomas. Identification of D₂ receptors in corticotroph tumors led to clinical trials of cabergoline therapy in limited cases of Nelson's syndrome, ectopic ACTH-secreting tumors, and recently Cushing's disease (CD).

Objective: To evaluate the long-term efficacy of cabergoline monotherapy in patients with CD.

Methods: Retrospective analysis of non-randomized clinical therapy with cabergoline in 30 patients with CD treated in academic centers of Buenos Aires and Montreal. Cabergoline was initiated at 0.5–1.0 mg/week and adjusted up to a maximal dose of 6 mg/week based on urinary free cortisol (UFC) levels. Complete response to cabergoline was defined as a sustained normalization of UFC with at least two normal values measured at 1–3 months interval; partial response was defined as a decrease of UFC to <125% of the upper limit of normal, and treatment failure as UFC ≥ 125% of it.

Results: Within 3–6 months, complete response was achieved in 11 patients (36.6%) and partial response in 4 patients (13.3%). After long-term therapy, nine patients (30%) remain with a complete response after a mean of 37 months (range from 12 to 60 months) with a mean dose of 2.1 mg/week of cabergoline. Two patients escaped after 2 and 5 years of complete response, but one patient transiently renormalized UFC after an increase in cabergoline dosage. No long-term response was maintained in four initial partial responders.

Conclusions: Cabergoline monotherapy can provide an effective long-term medical therapy for selected patients with CD, but requires close follow-up for dose adjustments.

European Journal of Endocrinology 163 709–716

Introduction

Cushing's disease (CD) is caused by ACTH-secreting pituitary adenomas in the majority of cases and is the most frequent etiology of endogenous Cushing's syndrome. The resulting hypercortisolism in CD is responsible for important cardiovascular, metabolic, and other morbidities (1).

Transsphenoidal surgery is the initial treatment of choice for most patients with CD. The therapeutic objectives of surgery include complete and selective resection of the ACTH-secreting pituitary adenoma, correction of the hypercortisolemic state and its complications, and maintenance of other pituitary functions (2). After a first surgery, remission rates reach 70–80% in patients from major centers as defined by suppressed plasma cortisol levels and normal 24 h urinary free cortisol (UFC), with concomitant resolution of clinical stigmata (2). Surgery success rates can reach 90% in selective adenomectomy of microadenomas but decrease to 65% in macroadenomas (1–3).

The long-term follow-up of patients with CD initially in remission following a first pituitary surgery reveals at 10 years a recurrence rate of 10–20% for subjects presenting with a microadenoma (2–4) and up to 45% for macroadenomas (1–3). Compared to the patients with microadenomas, clinical CD relapses with a shorter delay in subjects with larger tumors (3).

Management of persistent or recurrent CD is a challenge. In ultra specialized centers, a second pituitary surgery has a lower than 50% success rate in limited series and carries a high risk of hypopituitarism, often with undesirable effects on fertility (2, 5–7). Pituitary irradiation, either by conventional or by stereotactic radiotherapy, achieves eucortisolism in 50–60% of cases but with 3–5 years of delay (2). In addition, radiotherapy is associated with a high rate of pituitary insufficiency and possible risks of cognitive impairment, brain vascular morbidity, or secondary neoplasms (2). Bilateral adrenalectomy can also be utilized as a final approach and will control rapidly the clinical manifestations of CD, but it presents a non-negligible risk of

Nelson's syndrome (8–29%) and requires lifelong glucocorticoid/mineralocorticoid replacement (2, 8).

Some pharmacological therapies, mainly adrenal blocking agents, have also been used to control hypercortisolism, often as a bridge before surgery or while waiting for the effects of radiotherapy (2, 9, 10). However, steroidogenesis inhibitors or the adrenolytic agent mitotane have limited efficacy or cause side effects that restrain their long-term utilization.

A molecule specifically able to control ACTH production and corticotroph tumor growth would constitute a major improvement in the management of CD. Some pituitary-directed medical therapies have been proposed but provided inconsistent results (2). Studies using dopamine agonists like bromocriptine or cabergoline were initiated based on the demonstration of D₂ receptor expression in corticotroph tumors (11) and their ability to reduce ACTH and cortisol secretion in *in vitro* and *in vivo* studies (11–13). The effectiveness of bromocriptine was first reported in Nelson's syndrome and in the short-term treatment of CD with a shrinkage effect on pituitary tumors (14–17). However, long-term studies with bromocriptine demonstrated limited efficacy, with <30% of response during chronic treatment (9, 10, 18). For cabergoline, initial case reports and small sample size reported a similar ability to control ACTH and cortisol secretion in patients with Nelson's syndrome (19, 20) and ectopic ACTH-secreting tumors (21). A higher affinity and specificity of cabergoline for D₂ receptors in addition to its longer half-life (22, 23) could explain its better efficacy in CD, which have ranged from 25 to 75% in short course treatment of persistent or recurrent CD (24–29). Pivonello *et al.* (30) reported long-term effectiveness of cabergoline to control CD in 8 of 20 patients (40%) without significant side effects during 24 months of therapy. More recently, Vilar *et al.* (29) found a 25% complete response to cabergoline monotherapy in 12 CD patients receiving a maximal dose of 3 mg/week of cabergoline during 6 months; combination therapy with low dose of ketoconazole (200–400 mg/day) induced normalization of UFC in two-thirds of patients with persisting elevations of UFC.

The aim of the present study was to evaluate the long-term effects of cabergoline monotherapy in a cohort of 30 patients with CD including 3 patients as first-line therapy and 27 patients treated for persistent/recurrent CD.

Patients and methods

Thirty patients with CD were treated with cabergoline (25 females and 5 males; between 20 and 67 years of age) between 2002 and 2006 in the cohorts of the endocrinology divisions of the Hospital de Clinicas of the University of Buenos Aires (18 patients) and at the Centre Hospitalier de l'Université de Montréal (12 patients). Retrospective analysis of those cases was

performed. The initial diagnosis of CD was based upon i) elevated 24 h UFC levels with inappropriately normal/high plasma ACTH concentrations, ii) abnormal suppression of cortisol following low-dose and/or high-dose dexamethasone suppression tests, and iii) evidence of a pituitary source of ACTH during petrosal sinus sampling or a pituitary tumor on magnetic resonance imaging (MRI). Persistence or recurrence of CD after transsphenoidal surgery was defined as i) histological and immunohistological confirmation of corticotroph adenoma on the surgical specimen and ii) sustained elevation of UFC levels and abnormal suppression of cortisol following dexamethasone suppression test with clinical manifestations of hypercortisolism. At diagnosis or at time of relapse, before introduction of cabergoline, 24 h UFC varied from 105 to 692% of the upper limit of normal range with a mean at 283%. Six patients had documented concomitant hyperprolactinemia before treatment with 26, 27, 37, 45, 78, and 360 ng/ml (normal values below 25 ng/ml). At the time of initial diagnosis, a pituitary tumor was clearly identified in 23 cases (19 microadenomas and 4 macroadenomas), a radiological small microadenoma was suspected in 2 subjects, and none was detectable in 5 patients.

When cabergoline was introduced, no clear residual pituitary adenoma was identified in the majority of subjects with recurrent CD; two subjects had unrelated anomalies on the MRI: a hypothalamic vascular lesion and a post-surgical empty sella. Clinical and hormonal profiles of these two subjects were similar to other patients before introduction of cabergoline treatment. The initial clinical and biochemical profiles of all patients are shown in Table 1. Cabergoline was used as first-line therapy in three patients, and was introduced in the context of persistent or recurrent CD after initial pituitary surgery in 27 subjects. Cabergoline was introduced 9 months after initial pituitary surgery in two cases with residual disease. In other patients, cabergoline therapy was started between 2 and 17 years after relapse, which occurred after initial remission from first transsphenoidal surgery. For patient no. 22, cabergoline was introduced 4 years after initial pituitary surgery and 3 years after conventional pituitary radiotherapy.

Study design

Based on the initial reports on the efficacy of cabergoline in subjects with CD or Nelson's syndrome (11, 19, 20), patients with residual/persistent CD were offered cabergoline therapy after discussing the possible alternative modalities: a second pituitary surgery, radiotherapy, other medications (steroidogenesis inhibitors and adrenolytic agents), or bilateral adrenalectomy. Patients were informed about the off-label use of this drug for CD and gave oral consent to its administration to evaluate whether it could control their hypercortisolism. Cabergoline (Dostinex; Paladin

Table 1 Clinical and biochemical profile of 30 patients with CD before and after therapy with cabergoline.

Patient	Age (years)	Sex	Plasma ACTH (pg/ml) (NV: 10–55)	PRL (ng/ml) (NV: 3–25)	Values of UFC			Percent of normal UFC			Initial radiological finding	Initial therapy	Long-term response to cabergoline
					Basal	Under cabergoline (nmol/day)	Upper limit of normal	Basal (%)	Under cabergoline (%)				
1	34	F	158.0	7.3	1331	67	330	403	20	Microadenoma	TS, keto	Complete	
2	36	F	34.0	6.0	634	186	330	192	56	Microadenoma	TS	Complete	
3	31	F	90.0	10.9	459	186	330	139	56	Microadenoma	TS	Complete	
4	40	F	41.5	0.9 ^a	696	181	330	211	55	Microadenoma	TS	Complete	
5	31	F	23.0	10.6	522	231	330	158	70	Microadenoma	Caber	Complete	
6	22	M	28.7	8.4	128	87	90	142	97	Hypothalamic vasc. lesion	TS	Complete	
7	58	F	17.3	9.7	128	113	122	105	93	Arach.	TS	Complete	
8	53	F	93.0	23.0	198	81	90	220	90	No lesion ^b	TS	Complete	
9	67	F	220.0	–	297	77	90	330	86	Microadenoma	TS	Complete	
10	51	F	11.0	–	445	214	150	297	143	Microadenoma	TS	Complete/escape	
11	44	F	132.0	27.0	426	122	90	473	136	Macroadenoma	TS	Complete/escape	
Mean UFC in full responders													
12	42	M	43.0	3.0	307	165	90	341	183	Microadenoma	TS	Partial/escape	
13	30	F	175.0	26.0	309	459	90	343	510	Microadenoma	TS	Partial/escape	
14	44	F	41.5	20.0	131	192	122	107	157	No lesion ^b	TS	Partial/escape	
15	31	M	104.0	360.0	231	109	90	257	121	Microadenoma	TS	Partial	
Mean UFC in partial responders													
16	43	M	139.0	–	767	709	330	232	215	No lesion ^b	Caber	No response	
17	45	F	66.5	11.0	554	611	330	168	185	Microadenoma	TS	No response	
18	25	F	57.5	16.6	1307	1462	330	396	443	Microadenoma	TS	No response	
19	32	F	34.0	–	453	660	330	137	200	No lesion ^b	TS	No response	
20	20	M	50.0	13.0	545	847	330	165	257	Microadenoma	TS	No response	
21	47	F	–	–	637	870	330	193	264	Microadenoma	Caber	No response	
22	35	F	–	–	698	706	330	212	214	Microadenoma	TS-Rotx	No response	
23	23	F	10.0	11.8	423	614	123	344	499	Microadenoma	TS	No response	
24	21	F	7.0	–	151	189	100	151	189	Microadenoma	TS	No response	
25	41	F	26.0	37.0	830	1200	120	692	1000	Microadenoma	TS	No response	
26	40	F	33.0	78.0	504	706	90	560	784	Microadenoma	TS	No response	
27	28	F	126.0	–	275	181	90	306	201	Macroadenoma	TS	No response	
28	53	F	12.0	45.0	495	355	144	344	247	Macroadenoma	TS	No response	
29	61	F	13.0	16.0	227	280	90	252	311	No lesion ^b	TS	No response	
30	25	F	16.0	–	538	1010	90	598	1122	Macroadenoma	TS	No response	
Mean UFC in nonresponders													
Mean 39	25 F							317				30% of complete response	
Mean 5 M	5 M							283					

CD, Cushing's disease; UFC, urinary free cortisol; NV, normal value; PRL, prolactin; F, female; M, male; TS, transsphenoidal surgery; Keto, ketoconazole; Caber, cabergoline as first line; Vasc., vascular; Arach., arachnoidocele; Rotx, radiotherapy.

^aDecreased prolactin secondary to partial hypopituitarism after initial TS surgery in this patient.

^bNo lesion detected on MRI.

Laboratories, Montreal, Quebec, Canada and Pfizer, Buenos Aires, Argentina) was initiated at a dose of 0.5–1.0 mg/week and was increased progressively by 0.5 or 1.0 mg/week at 1 or 2 months interval until complete and sustained normalization of UFC levels. As there was no formal protocol, the treating physicians decided on an individual basis to stop or increase the dose of cabergoline up to a maximal dose of 6 mg/week. All patients with CD who received cabergoline in the two centers were included in the retrospective analysis. Review of the charts of the 30 subjects focused on the long-term effects of cabergoline treatment, biochemical and clinical features of CD, as well as the possible side effects reported by the patients. Plasma ACTH and prolactin (PRL) concentrations were measured at each center by immunometric assay, whereas serum and UFC levels were determined using enzyme immunoassay or RIA after extraction with dichloromethane.

Criteria of response to treatment

During evaluation and follow-up of patients, UFC was measured successively during one to three 24 h periods at intervals of 1–2 months based on clinical indications. Complete response to cabergoline was defined as normalization of the mean UFC levels at time of assessment. A decrease in UFC to <125% of the upper limit of normal range but without complete normalization was considered as a partial response to cabergoline. Patients with UFC $\geq$ 125% of the upper limit of normal range were classified as nonresponders. A re-increase in UFC over the upper limit of normal range after initial normalization with cabergoline was considered an escape to treatment.

Statistical analysis

Data for UFC are presented as means $\pm$ s.d. and percentage of upper limit of normal. Student's *t*-test was used to compare baseline and post-treatment values. Statistical significance was defined as *P* values <0.05.

Results

Initial response to treatment

Within 3–6 months of therapy, complete response of UFC was achieved in 11 patients (36.6%) and partial response in 4 patients (13.3%), representing 50% of the cohort. Mean cabergoline dose used was 1.5 mg/week with a range from 0.5 to 4.0 mg/week. Complete normalization of UFC in full responders took an average of 4.2 months with progressive increase in cabergoline doses.

Fifteen subjects were unresponsive to cabergoline treatment with minimal change in UFC and persistent symptoms and signs of CD. For the nonresponders, UFC

tended to increase by a mean of 35.2% during cabergoline use with an average dose of 2.0 mg/week (range of 1.0–4.5 mg/week); in this subgroup, cabergoline was used for a mean of 4.0 months (from 1 to 9 months).

For the three subjects in whom cabergoline was used as first-line therapy, one patient demonstrated a complete normalization of UFC after 1 month of treatment with 1.0 mg/week of cabergoline. This subject is still in full response for UFC with regression of clinical signs for a total of 18 months of treatment with a current dose of 0.5 mg/week. The dose of cabergoline was reduced to limit possible adrenal insufficiency. The two other patients on first-line therapy did not respond after 3 months of treatment with 1.5 or 2.0 mg/week of cabergoline.

Long-term response to treatment

At final analysis, 9 of the initial 11 full responders maintained a eucortisolic state after a mean duration of 37 months of treatment (from 12 to 60 months) with a mean dose of 2.1 mg/week of cabergoline (range from 0.5 to 6.0 mg/week; Fig. 1). Clinical symptoms and signs of CD regressed progressively in full responders. An escape phenomenon was observed in two patients with initial complete normalization of UFC after 2 years of treatment with 2.5 mg/week and after 5 years with 1.5 mg/week of cabergoline respectively (Fig. 2). In the second subject, increasing the cabergoline dose up to 6.0 mg/week restored normal values of UFC after 78 months of treatment, but UFC recently increased again to 136% of normal after 84 months. This patient's pituitary macroadenoma regressed by more than 50% with the initial 1.5 mg/week dose of cabergoline;

Figure 1 Complete long-term response to cabergoline monotherapy in nine patients with CD.

Figure 2 Detailed response to cabergoline in two patients with CD who presented an escape phenomenon.

a regrowth of the macroadenoma occurred during the escape phenomenon but decreased in size again following increase of cabergoline to 6.0 mg/week dose (31). Partial response to cabergoline was noted initially in four subjects, but after 6 months of treatment, these four patients increased their UFC over or close to 125% of the upper limit of normal range, even if, for two cases, cabergoline doses were increased. However, the average dose used in those cases was only 2.0 mg/week.

Including the two subjects with late escape phenomenon as failures, long-term and complete response to cabergoline was achieved in 30% of our cohort with a mean dose and length of treatment of 2.1 mg/week over 37 months. In our study population, neither initial size of tumor, timing of cabergoline introduction (prior to surgery or rapidly after the intervention), ACTH levels, nor the initial severity of hypercortisolism was predictive of the response. No difference was noted in UFC before starting cabergoline therapy between the three outcome groups, with a mean UFC of 243% for patients with an initial complete response to cabergoline, 262% for partial responders, and 317% for nonresponders ($P > 0.05$). Detailed appreciation of cabergoline effect on tumor growth was not possible since the majority of patients of this cohort did not have measurable residual adenomas on MRI following surgery.

PRL was suppressed with cabergoline treatment in all patients in whom it was monitored. The three patients with initial hyperprolactinemia (twice the upper limit of normal) did not achieve normalization of UFC with cabergoline therapy.

Tolerance to cabergoline therapy

No major adverse events or side effects were reported. Transient dizziness and nausea were noted during initiation of cabergoline therapy in three patients but did not require drug withdrawal. No symptoms of cardiovascular dysfunction were reported during the period of treatment. During their follow-up, eight patients had an echocardiography performed, and none demonstrated the presence of significant cardiac valvulopathy. No patient presented symptomatic adrenal insufficiency secondary to cabergoline therapy.

Discussion

The present study confirms that short-term treatment of patients with CD with cabergoline improves cortisol secretion in 50% of subjects, with complete normalization of UFC in 36.6% of cases. Long-term follow-up during a mean period of 37 months demonstrated sustained effectiveness of cabergoline in 30% of subjects with mostly persistent or recurrent CD. Only two patients with initial complete response presented an escape phenomenon but only after 2.5 and 5 years of treatment. Restoration of a complete response by increasing the dose of cabergoline was possible only transiently in one of the two patients, but her last UFC value increased slightly above normal range. In subjects with incomplete initial response to cabergoline (first 3–6 months), extension of treatment to over 1 year did not achieve complete or sustained normalization of UFC.

Our results are similar to those reported by the group of Pivonello *et al.* (30) who demonstrated a sustained response to cabergoline in 40% of subjects over a mean period of treatment of 24 months with an average dose of 3.5 mg/week (range from 1 to 7 mg/week). In their study, initial response to cabergoline was even higher as they found complete normalization of cortisol secretion in 15 of their 20 patients (75%) after 3–6 months of treatment. Their escape rate was higher than that observed in our study; however, our finding of a 30% complete response rate after a mean of 37 months of therapy and in some cases maintained for more than 60 months clearly extends the demonstration of long-term efficacy of cabergoline in selected patients with CD. It should be noted that 40% of their subjects demonstrated initial mild hyperprolactinemia (30), but we found no correlation between basal PRL levels and response of UFC to cabergoline therapy in our study. The more modest 25% complete response rate in CD patients studied by Vilar *et al.* (29) could result from their maximal cabergoline dose of 3.0 mg/week.

We used cabergoline as first-line therapy in only three patients of the cohort. One subject still presents a complete response to cabergoline and stabilization of the microadenoma on MRI. There is only very limited data about cabergoline as first-line therapy in CD, but its

safety profile, relative efficacy, and surgery-sparing potential appear to warrant the conduct of prospective studies on its long-term efficacy in larger cohorts of patients with CD; it could be a particularly interesting first-line therapeutic option for patients with radiologically non-detectable CD.

There are several limitations of the present report, which are mostly related to its design as a retrospective study without a systematic therapeutic and monitoring protocol. Thus, a maximal dosage of 6.0 mg/week was not reached in over 80% of patients with initial partial response or nonresponse to cabergoline, potentially underestimating the maximal efficacy of cabergoline therapy. Even if full response to cabergoline occurred at a low dose in some subjects, an increase in the dose of cabergoline became necessary in other patients in whom UFC escaped after initial response (patient no. 11 in Fig. 2). Larger number of patients will be required to establish a possible relationship between degree of hypercortisolism, cabergoline dosage, and response to treatment. Cyclic CD could also be considered to explain fluctuations in UFC and required dose of cabergoline to control CD; however, in our two patients with an escape phenomenon, this appears unlikely when considering the initial length of response lasting 2 and 5 years. It is more likely that the escape phenomenon would result from progressive selection and growth of corticotroph cells not expressing high levels of D₂ receptors. In this report, two distinct populations of patients in two countries were studied, and UFC was measured in different laboratories but, for each subject, the same assay and laboratory were used for their serial UFC.

One main concern about cabergoline utilization is its potential side effects. No major hypotension or severe asthenia reported in previous studies (30, 32) was documented among patients in this cohort. Even if all patients of this cohort did not systematically undergo an echocardiography before and during therapy, none of the subjects evaluated during longer successful use of cabergoline developed echocardiographic evidence of cardiac dysfunction or valvulopathy. Recent studies found that patients with Parkinson's disease treated with cabergoline had an increased prevalence of cardiac valve insufficiency (33, 34). However, higher doses of cabergoline were used in Parkinson's disease patients, an older population than patients with CD. The length of therapy in this study is also shorter compared with long-term treatment used in Parkinson's disease and could explain the lack of valvular disease in our group and in the 20 patients with CD reported by Pivonello *et al.* (30). Long-term follow-up to evaluate the risk of development of valvulopathy is thus indicated.

Cabergoline was described as having potential positive metabolic effects. Similar to other dopamine receptor agonists, it could lower blood pressure and improve glucose tolerance independent of its cortisol lowering effect. Dopamine agonists lower peripheral resistance, relaxing vascular wall smooth muscles, with

consequent improvement of blood pressure (32). Also, bromocriptine improved glucose homeostasis in type 2 diabetes patients by stimulating splanchnic glucose reuptake and by helping insulin-mediated suppression of hepatic glucose production (35).

Recent studies have also demonstrated a predominance of somatostatin receptor subtype 5 in corticotroph adenomas as well as co-expression of dopamine receptors in some tumors; pasireotide, a multi-somatostatin receptor analog, was found to inhibit ACTH secretion from corticotroph adenomas *in vitro* (36). Recently, Boscaro *et al.* (37) showed that short-term 15 day administration of pasireotide improved or normalized UFC in 76% of patients with *de novo* or persistent CD; the long-term effects of this drug are currently under investigation, but appears to have potential long-term efficacy (38). In a proof-of-concept pilot study, Feelders *et al.* (39) recently found that the sequential combination of low-dose pasireotide, followed, if UFC remained elevated, by cabergoline up to 4.5 mg/week during 80 days, could achieve complete response rate of 53% in a group of 17 patients with *de novo* CD; the sequential addition of ketoconazole if UFC remained elevated achieved normalization of UFC in 88% of patients.

In conclusion, our study confirms that cabergoline is a valid therapeutic option as it provides long-term complete response in 30% of patients mostly with persistent or recurrent CD and presents a reassuring safety profile. Additional prospective studies with larger number of patients are needed to corroborate those conclusions and to validate predictive factors for the identification of patients susceptible to respond to cabergoline. Further studies using cabergoline in monotherapy or in combination with pasireotide should provide exciting new strategies for medical treatment of *de novo* or recurrent CD.

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.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

- 1 Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A & Boscaro M. Diagnosis and complications of Cushing's syndrome: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 5593–5602. (doi:10.1210/jc.2003-030871)
- 2 Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus AR, Hofland LJ,

- Klibanski A, Lacroix A, Lindsay JR, Newell-Price J, Nieman LK, Petersenn S, Sonino N, Stalla GK, Swearingen B, Vance ML, Wass JA & Boscaro M. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 2454–2462. (doi:10.1210/jc.2007-2734)
- 3 De Tommasi C, Vance ML, Okonkwo DO, Diallo A & Laws ER Jr. Surgical management of adrenocorticotrophic hormone-secreting macroadenomas: outcome and challenges in patients with Cushing's disease or Nelson's syndrome. *Journal of Neurosurgery* 2005 **103** 825–830. (doi:10.3171/jns.2005.103.5.0825)
- 4 Atkinson AB, Kennedy A, Wiggam MI, McCance DR & Sheridan B. Longterm remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. *Clinical Endocrinology* 2005 **63** 549–559. (doi:10.1111/j.1365-2265.2005.02380.x)
- 5 Benveniste RJ, King WA, Walsh J, Lee JS, Delman BN & Post KD. Repeated transsphenoidal surgery to treat recurrent or residual pituitary adenoma. *Journal of Neurosurgery* 2005 **102** 1004–1012. (doi:10.3171/jns.2005.102.6.1004)
- 6 Friedman RB, Oldfield EH, Nieman LK, Chrousos GP, Doppman JL, Cutler GB Jr & Loriaux DL. Repeat transsphenoidal surgery for Cushing's disease. *Journal of Neurosurgery* 1989 **71** 520–527. (doi:10.3171/jns.1989.71.4.0520)
- 7 Hofmann BM, Hlavac M, Kreutzer J, Grabenbauer G & Fahlbusch R. Surgical treatment of recurrent Cushing's disease. *Neurosurgery* 2006 **58** 1108–1118. (doi:10.1227/01.NEU.0000215945.26764.92)
- 8 Assie G, Bahurel H, Coste J, Silvera S, Kujas M, Dugue MA, Karray F, Dousset B, Bertherat J, Legmann P & Bertagna X. Corticotroph tumor progression after adrenalectomy in Cushing's disease: a reappraisal of Nelson's syndrome. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 172–179. (doi:10.1210/jc.2006-1328)
- 9 Miller JW & Crapo L. The medical treatment of Cushing's syndrome. *Endocrine Reviews* 1993 **14** 443–458. (doi:10.1210/edrv-14-4-443)
- 10 Nieman LK. Medical therapy of Cushing's disease. *Pituitary* 2002 **5** 77–82. (doi:10.1023/A:1022308429992)
- 11 Pivonello R, Ferone D, De Herder WW, Kros JM, Del Basso De Caro MM, Arvigo M, Annunziato L, Lombardi G, Colao A, Hofland LJ & Lamberts SWJ. Dopamine receptor expression and function in corticotroph pituitary tumors. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 2452–2462. (doi:10.1210/jc.2003-030837)
- 12 De Bruin C, Hanson JM, Meij BP, Kooistra HS, Waaijers AM, Uitterlinden P, Lamberts SWJ & Hofland LJ. Expression and functional analysis of dopamine receptor subtype 2 and somatostatin receptor subtypes in canine Cushing's disease. *Endocrinology* 2008 **149** 4357–4366. (doi:10.1210/en.2008-0244)
- 13 Castillo VA, Gómez NV, Lalia JC, Cabrera Blatter MF & Garcia JD. Cushing's disease in dogs: cabergoline treatment. *Research in Veterinary Science* 2007 **85** 26–34. (doi:10.1016/j.rvsc.2007.08.009)
- 14 Lamberts SW & Birkenhager JC. Bromocriptine in Nelson's syndrome and Cushing's disease. *Lancet* 1976 **2** 811. (doi:10.1016/S0140-6736(76)90656-5)
- 15 Lamberts SW, Klinjn JG, De Quijada M, Timmermans HA, Uitterlinden P, De Jong FH & Birkenhager JC. The mechanism of the suppressive action of bromocriptine on adrenocorticotropin secretion in patients with Cushing's disease and Nelson's syndrome. *Journal of Clinical Endocrinology and Metabolism* 1980 **51** 307–311. (doi:10.1210/jcem-51-2-307)
- 16 Invitti C, De Martin M, Danesi L & Cavagnini F. Effect of injectable bromocriptine in patients with Cushing's disease. *Experimental and Clinical Endocrinology and Diabetes* 1995 **103** 266–271. (doi:10.1055/s-0029-1211361)
- 17 Bevan JS, Webster J, Burke CW & Scanlon ME. Dopamine agonist and pituitary tumor shrinkage. *Endocrine Reviews* 1992 **13** 220–240. (doi:10.1210/edrv-13-2-220)
- 18 Mercado-Asis LB, Yasuda K, Murayama M, Mune T, Morita H & Miura K. Beneficial effects of high daily dose bromocriptine treatment in Cushing's disease. *Endocrinologia Japonica* 1992 **39** 385–395.
- 19 Pivonello R, Faggiano A, Di Salle F, Filippella M, Lombardi G & Colao A. Complete remission of Nelson's syndrome after 1-year treatment with cabergoline. *Journal of Endocrinological Investigation* 1999 **22** 860–865.
- 20 Casulari LA, Naves LA, Mello PA, Pereira Neto A & Papadia C. Nelson's syndrome: complete remission with cabergoline but not with bromocriptine or cyproheptadine treatment. *Hormone Research* 2004 **62** 300–305. (doi:10.1159/000082235)
- 21 Pivonello R, Ferone D, de Herder WW, Faggiano A, Bodei L, de Krijger RR, Lombardi G, Colao A, Lamberts SW & Hofland LJ. Dopamine receptor expression and function in corticotroph ectopic tumors. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 65–69. (doi:10.1210/jc.2006-0728)
- 22 Colao A, Di Sarno A, Pivonello R, Di Somma C & Lombardi G. Dopamine receptor agonists for treating prolactinomas. *Expert Opinion on Investigational Drugs* 2002 **11** 787–800. (doi:10.1517/13543784.11.6.787)
- 23 Colao A, Lombardi G & Annunziato L. Cabergoline. *Expert Opinion on Pharmacotherapy* 2000 **1** 555–574. (doi:10.1517/14656566.1.3.555)
- 24 Manavela M, Danilowicz K & Bruno OD. Cabergoline effect in ACTH-dependent Cushing's syndrome. 12th International Congress of Endocrinology, Lisbon, Portugal, Poster-867, pp 302, August 31–September 4, 2004.
- 25 Miyoshi T, Otsuka F, Takeda M, Inagaki K, Suzuki J, Ogura T, Date I, Hashimoto K & Makino H. Effect of cabergoline treatment on Cushing's disease caused by aberrant adrenocorticotropin-secreting macroadenoma. *Journal of Endocrinological Investigation* 2004 **27** 1055–1059.
- 26 Illouz F, Dubois-Ginouvès S, Laboureaux S, Rohmer V & Rodien P. Use of cabergoline in persisting Cushing's disease. *Annales d'Endocrinologie* 2006 **67** 353–356. (doi:10.1016/S0003-4266(06)72611-7)
- 27 Godbout A, Beauregard H & Lacroix A. Cabergoline in the long-term treatment of Cushing's Disease. The Endocrine Society's 89th Meeting, Toronto, Ontario, Abstract P4–51, June 2–5, 2007.
- 28 Godbout A, Manavela M, Danilowicz K, Beauregard H, Bruno OD & Lacroix A. Long-term therapy with cabergoline in Cushing's disease. The Endocrine Society's 90th Meeting, San Francisco, Abstract P2–130, June 15–18, 2008.
- 29 Vilar L, Naves LA, Azevedo ME, Arruda MJ, Arahata CM, Moura E, Silva L, Agra R, Pontes L, Montenegro L, Albuquerque JL & Canadas V. Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease. *Pituitary* 2010 **13** 123–129. (doi:10.1007/s11102-009-0209-8)
- 30 Pivonello R, De Martino MC, Cappabianca P, De Leo M, Faggiano A, Lombardi G, Hofland LJ, Lamberts SWJ & Colao A. The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 223–230. (doi:10.1210/jc.2008-1533)
- 31 Manavela M, Danilowicz K & Bruno OD. Macrocorticotropina shrinkage and biochemical control under long-term cabergoline therapy. *Proceedings European Neuroendocrine Association workshop on Novel Insights in the management of Cushing's syndrome*, Napoli. Abstract 38, pp 57, December 4–6, 2009.
- 32 Murphy MB. Dopamine: a role in the pathogenesis and treatment of hypertension. *Journal of Human Hypertension* 2000 **14** S47–S50. (doi:10.1038/sj.jhh.1000987)
- 33 Schade R, Andersohn F, Suissa S, Haverkamp W & Garbe E. Dopamine agonist and the risk of cardiac-valve regurgitation. *New England Journal of Medicine* 2007 **356** 29–38. (doi:10.1056/NEJMoa062222)

- 34 Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S & Pezzoli G. Valvular heart disease and the use of dopamine agonist for Parkinson's disease. *New England Journal of Medicine* 2007 **356** 39–46. (doi:10.1056/NEJMoa054830)
- 35 Pijl H, Ohasshi S, Matsuda M, Miyazaki Y, Mahankali A, Kumar V, Pipek R, Iozzo P, Lancaster JL, Cincotta AH & DeFronzo RA. Bromocriptine: a novel approach to the treatment of type 2 diabetes. *Diabetes Care* 2000 **23** 1154–1161. (doi:10.2337/diacare.23.8.1154)
- 36 De Bruin C, Pereira AM, Feelders RA, Romijn JA, Roelfsema F, Sprij-Mooij DM, Van Aken MO, Van Der Lelij AJ, De Herder WW, Lamberts SW & Hofland LJ. Coexpression of dopamine and somatostatin receptor subtypes in corticotroph adenomas. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1118–1124. (doi:10.1210/jc.2008-2101)
- 37 Boscaro M, Ludlam WH, Atkinson B, Glusman JE, Petersenn S, Reincke M, Snyder P, Tabarin A, Biller BM, Findling J, Melmed S, Darby CH, Hu K, Wang Y, Freda PU, Grossman AB, Frohman LA & Bertherat J. Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 115–122. (doi:10.1210/jc.2008-1008)
- 38 Boscaro M, Zhang Y, Sen K, Maldonado M, Schoenherr U & Findling J. Long-term treatment of Cushing's disease with pasireotide (SOM230): results from a phase II extension study. The Endocrine Society's 92th meeting, San Diego, P1–274, June 19–22, 2010.
- 39 Feelders RA, de Bruin C, Pereira AM, Romijn JA, Netea-Maier RT, Hermus AR, Zelissen PM, van Heerebeek R, de Jong FH, van der Lely AJ, de Herder WW, Hofland LJ & Lamberts SW. Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. *New England Journal of Medicine* 2010 **362** 1846–1848. (doi:10.1056/NEJMc1000094)

Received 27 July 2010

Accepted 11 August 2010