Medical treatment of prolactinomas

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Abstract | Prolactinomas, the most prevalent type of neuroendocrine disease, account for approximately 40% of all pituitary adenomas. The most important clinical problems associated with prolactinomas are hypogonadism, infertility and hyposexuality. In patients with macroprolactinomas, mass effects, including visual field defects, headaches and neurological disturbances, can also occur. The objectives of therapy are normalization of prolactin levels, to restore eugonadism, and reduction of tumor mass, both of which can be achieved in the majority of patients by treatment with dopamine agonists. Given their association with minimal morbidity, these drugs currently represent the mainstay of treatment for prolactinomas. Novel data indicate that these agents can be successfully withdrawn in a subset of patients after normalization of prolactin levels and tumor disappearance, which suggests the possibility that medical therapy may not be required throughout life. Nevertheless, multimodal therapy that involves surgery, radiotherapy or both may be necessary in some cases, such as patients who are resistant to the effects of dopamine agonists or for those with atypical prolactinomas. This Review reports on efficacy and safety of pharmacotherapy in patients with prolactinomas.

Introduction

Prolactin-secreting adenomas are the most predominant type of all pituitary tumors. The estimated prevalence is 100 prolactinomas per million adults,[1] although Ciccarelli *et al.*[2] reported an even higher prevalence of 775 per million adults in Belgium. The incidence of prolactinomas varies with age and sex; these tumors occur with the highest frequency in women aged 20–50 years, at which point the ratio between the sexes is estimated to be 10:1. In adults aged >60 years, prolactinomas occur with a similar frequency in both sexes.[3,4] During childhood, pituitary tumors are rare; however, prolactinomas constitute about 50% of all pituitary adenomas in this subpopulation.[5]

The most important clinical symptoms of prolactin excess are gonadal and sexual dysfunction as a result of tumor expansion in patients with macroadenomas.[6] Medical therapy of prolactinomas relies on the use of dopamine receptor agonists, such as bromocriptine, cabergoline and quinagolide. Given the evidence-based efficacy of these agents, other dopamine agonists, for example, lisuride and terguride, as well as the serotonin antagonist metergoline, are rarely used. The dopamine agonist pergolide has been removed from the market because of detrimental effects on cardiac valves. In patients with prolactinomas, the main aims of treatment are the control of hormone excess and shrinkage of the tumor mass, together with prevention of their clinical consequences. At the same time, residual pituitary function must be preserved or improved, and tumor recurrence or disease progression should be prevented.[1]

Marked growth of untreated microprolactinomas (<10 mm in diameter) is uncommon. Treatment of asymptomatic patients with prolactinomas is, therefore, not always necessary.[6,7] Importantly, patients with macroprolactinomas (>10 mm in diameter) and hypopituitarism should receive standard hormone replacement therapy, the same as any other patient with hormone deficiencies. Two exceptions to this statement exist. Initiation of growth hormone (GH) and gonadal steroid replacement should be delayed until after normoprolactinemia and/or tumor shrinkage are achieved,[8] given that both GH and gonadal steroid deficiencies can be restored by normalization of prolactin levels compared with other deficiencies of the pituitary axis.

This Review summarizes the data on medical treatment of patients with prolactinomas. In particular, we will focus on previous findings of an association between cardiac valve disease and treatment with dopamine agonists in patients with hyperprolactinemia and on the possibility that permanent control of prolactin levels can be achieved after withdrawal from these drugs.

Treatment profile of dopamine agonists

Dopamine agonists can be divided into two classes: the ergot derivatives, which include bromocriptine, pergolide and cabergoline, and the non-ergot derivatives, for example, quinagolide. Treatment with dopamine agonists causes a clinically relevant decrease in the size of prolactinomas through a number of mechanisms. First, by reducing cell volume indirectly through inhibition of hormone secretion in an early phase; second, via inhibition of gene transcription and prolactin synthesis at a later stage; and finally, by inducing perivascular fibrosis

Competing interests
The authors declare no competing interests.

Key points

- Medical treatment of prolactinomas with cabergoline, quinagolide or bromocriptine is very efficacious; cabergoline has demonstrated superiority in efficacy to other drugs in many studies

- Cardiac valve disease induced by cabergoline treatment in patients with hyperprolactinemia is still a matter of debate

- In the absence of unequivocal proof excluding a negative effect of cabergoline in patients with hyperprolactinemia, all patients who receive long-term cabergoline treatment should undergo regular echocardiographic follow-up

- Long-term discontinuation of cabergoline or bromocriptine in patients with hyperprolactinemia of any cause has shown a variable rate of tumor recurrence; predictors of recurrence before cabergoline withdrawal are tumor diameter and prolactin levels

- Resistance to dopamine agonists is a rare phenomenon that characterizes a group of tumors that generally manifest with a more aggressive behavior than usual

and cell necrosis.[9] A more extensive discussion of this topic can be found elsewhere.[6,10]

Bromocriptine

Bromocriptine, the oldest drug for medical treatment of prolactinomas, was introduced into clinical practice 25 years ago.[6,9–11] This ergot alkaloid is derived by semi-synthesis and has D_2 receptor agonist and D_1 receptor antagonist properties. Although the most widely used drug in patients with hyperprolactinemia is cabergoline, bromocriptine is still frequently prescribed as the best alternative to cabergoline.[12] Compared with cabergoline, bromocriptine has a shorter half-life and is administered two or three times daily. Once daily administration may be recommended in some patients who are highly sensitive to the drug. The therapeutic dose generally ranges between 2.5 mg and 15.0 mg per day, with most patients receiving 7.5 mg or less.[13–19] In patients with treatment resistance, bromocriptine doses can be increased to 20–30 mg per day.[17]

In 80–90% of patients with microprolactinomas and in 70% of individuals with macroprolactinomas, bromo-criptine treatment controls hyperprolactinemia and thus restores gonadal function and reduces tumor size.[10,11] Tumor mass effects, such as headaches and visual field defects, improve within days after initiation of bromo-criptine therapy in most patients. Notably, gonadal and sexual function can ameliorate even if prolactin levels are still above the normal range. In general, prolactinomas remain sensitive to bromocriptine and delayed resistance is rare; however, treatment withdrawal can often result in recurrence of hyperprolactinemia (see below). Normalization of prolactin levels is followed by improvements in BMD, both in women[13] and in men,[15] and improvement of semen quality.[20]

Adverse effects of bromocriptine include nausea, vomiting, postural hypotension, headache and dizziness, which are caused by the rapid intestinal absorption of the drug. In the past, various formulations of bromocriptine were developed to improve tolerability, for example, long-acting and repeatable formulations for intramuscular injection, an intranasal powder formulation or tablets for intravaginal administration. Despite initial promising data,[21,22] none of these formulations has been introduced into the market.

Cabergoline

In contrast with bromocriptine, which has a partial affinity for the D_1 receptor, cabergoline is a selective D_2 eceptor agonist with widely known beneficial effects in resolving hyperprolactinemia.[23] Chronic cabergoline treatment at a twice-weekly dose of 1 mg significantly reduces serum prolactin levels in up to 95% of women with hyperprolactinemia.[24] In a large study that included data from 455 patients,[25] cabergoline treatment achieved normalization of prolactin levels in 86% of 425 patients, that is, in 92% of 244 patients with idiopathic hyper-prolactinemia or microprolactinomas and in 77% of 181 patients with macroprolactinomas. Only 13% of the patients included in this study reported clinically rele-vant adverse effects, and only 4% of all patients discon-tinued treatment as a result of these adverse events.[25] In a comparative retrospective study by Di Sarno *et al.*,[26] the efficacy of cabergoline was demonstrated to be greater than that obtained using bromocriptine.

At treatment start, the median dose of cabergoline is usually 0.5 mg per week in patients with idiopathic hyperprolactinemia or microprolactinomas.[26] For indivi-duals with macroprolactinomas, treatment with caber-goline should be initiated at very low doses (0.25 mg weekly) to avoid a too rapid effect on tumor shrink-age,[27,28] as this emergency condition can cause intra-tumoral hemorrage that requires immediate surgical intervention. The dosage is then increased according to the individual patient's condition in order to control pro-lactin excess. After 12–24 months of cabergoline therapy, a reduction in tumor mass (by ≥20% compared with baseline values) is observed in >80% of cases, whereas total tumor disappearance occurs in 26–36% of patients. Cabergoline treatment of patients previously treated with bromocriptine or quinagolide has been reported to cause a further shrinkage of the tumor in the major-ity of individuals, even in those considered resistant to dopamine agonists.[29] As expected, the rate of control of prolactin excess and decline in tumor size was higher in drug-naive patients than in previously treated indivi-duals (Figure 1).[29] Available data of cabergoline treat-ment in men with hyperprolactinemia are still limited, as prolactinomas in men are rarer than in women.[6,30] However, the efficacy of cabergoline treatment has been demonstrated in male patients, not only for the control of prolactin levels and tumor size,[31] but also for the improvement of fertility by normalizing sperm quality[20,31] and sexual function.[32] In less than 5% of the patients, hyperprolactinemia may persist despite increas-ing cabergoline dosage.[17,33–36] Some studies have reported negative effects of cabergoline on cardiac valves. These data are discussed in a following section.

Quinagolide

Quinagolide, a non-ergot derived dopamine agonist with selective D_2 receptor activity, is available for oral

administration in a single daily dose. In women with hyperprolactinemia, quinagolide treatment is reported to control prolactin excess and tumor growth.[37] In 13 of 14 men with hyperprolactinemia and associated abnormalities of sperm quality, treatment with quinagolide over 3 months was associated with normalization of prolactin levels and sperm parameters.[38] In addition, quinagolide treatment caused a reduction of tumor mass by at least 30% from baseline size in 8 of 13 men with macroprolactinomas.[38] Moreover, quinagolide treatment over 24 weeks decreased tumor size in 21 patients, as well as restored regular menses in 11 of 15 premenopausal women and sexual function in five of seven men enrolled in a prospective, multicenter trial.[39]

On the basis of these results, quinagolide treatment might be considered as effective as bromocriptine treatment. After 24 weeks, 81% of patients experienced biochemical control of prolactin excess with quinagolide compared with 70% with bromocriptine. Both drugs restored menses and fertility and controlled galactorrhea in a similar proportion of patients;[39] however, the safety profile was more favorable for quinagolide.[39,40] Nonetheless, compared with cabergoline, quinagolide was less efficacious and adverse effects were more frequent,[26,41,42] although quinagolide does not seem to induce cardiac valve disease.[43] Quinagolide is currently available for treatment of hyperprolactinemia in several European countries and in Canada but not in the USA.

Other drugs

Pergolide, an ergot derivate with D_1 and D_2 agonist activity approximately 100-fold that of bromocriptine, controlled prolactin excess and reduced tumor size in the majority of newly diagnosed patients with macroprolactinomas.[44,45] However, pergolide was withdrawn from the market in 2007 because of adverse effects on cardiac valves.

Lisuride hydrogen maleate, another ergot derivate, was investigated for its ability to inhibit prolactin secretion in experimental hyperprolactinemia.[46,47] Terguride, an analogue of lisuride, normalized prolactin levels and reduced tumor mass in a limited number of patients with microprolactinomas.[48] Metergoline, a 5-hydroxytryptamine receptor 1B (HTR1B) and HTR1D antagonist, was also used to prevent lactation in the past.

Cardiac valve disease

The safety of pergolide and cabergoline has been questioned given the results of two studies in patients with Parkinson disease, which showed an increased risk of valve regurgitation, that is, the abnormal seeping of blood from the ventricle, through the valve, into the atrium when the ventricle contracts, which causes regurgitation of blood back into the atrium.[49,50] Besides its affinity for D_2 dopamine receptors, cabergoline also possesses a high affinity for HTR2B, a receptor located on heart valves. Activation of HTR2B can lead to mitogenesis and fibroblast proliferation, which in turn can cause thickening, retraction and stiffening of the valve apparatus. These changes induce inadequate closure of
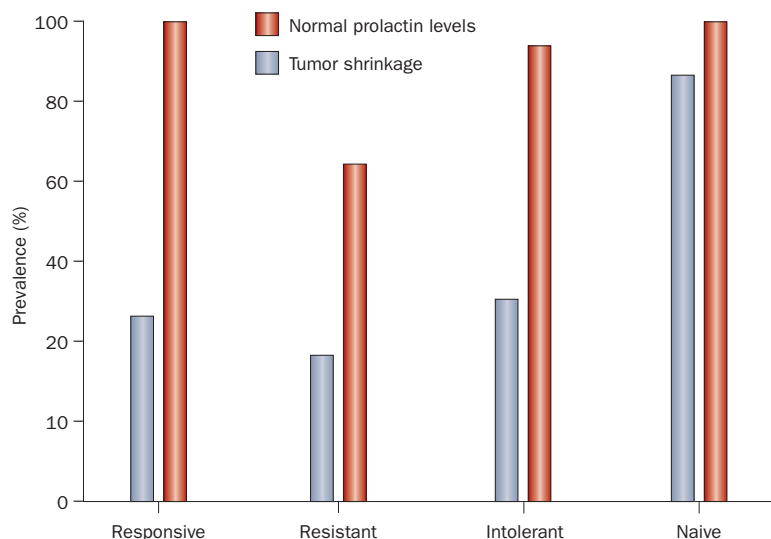

Figure 1 | Prevalence of normal prolactin levels and of tumor shrinkage >80% compared to basal volume in patients with macroprolactinomas grouped according to previous treatment with bromocriptine or quinagolide and then treated with cabergoline (0.25–3.5 mg weekly) for 1–3 years. Responsive: 28 patients, previously treated with bromocriptine or quinagolide for 1–5 years, who achieved normoprolactinemia and restoration of gonadal function, but no longer treated with these drugs because of poor compliance or because the drug was not longer available. Resistant: 37 patients shown to be resistant or hyporesponsive to bromocriptine, quinagolide or both. Intolerant: 19 patients previously shown to be intolerant to bromocriptine treatment. Naive: 26 untreated patients. Figure is based on data from Colao and colleagues.[29]

the valves and clinically relevant regurgitation that is asymptomatic in most cases.

On histopathology, cardiac valves from patients treated with pergolide or cabergoline for Parkinson disease show abnormalities similar to those found in patients with carcinoid disease who are treated with ergot alkaloid drugs (ergotamine, methysergide) against migraine or anorectic drugs (fenfluramine).[51] In the healthy population, the prevalence of valve regurgitation is highly variable, ranging from 24% to 96% for tricuspid regurgitation and between 10% and 80% for mitral regurgitation.[52,53] Clearly, population studies include patients with hypertension as well as those with other cardiac risk factors, thus, their results are hardly comparable with those of patients with hyperprolactinemia, who are predominantly women of young age.[54]

Nevertheless, 11 studies assessed the potential association between valve regurgitation and the use of cabergoline in patients treated for prolactinoma (Table 1). In total, 795 patients treated with cabergoline at a median cumulative dose of 290 mg and a median duration of 59 months and 1,202 healthy control individuals were included in these studies. Five of these studies did not report any relevant cardiac findings, although increased prevalence of regurgitation in any valve was reported in five studies, and one study reported an increased tenting area of the mitral valve (Table 1). We have reported an increased risk of tricuspid regurgitation in patients treated with cabergoline over at least 1 year, with a small but significant association with higher

Table 1 | Cardiac valve disease in patients with hyperprolactinemia treated with cabergoline

Author	Year	Patients	Controls	Cumulative dose (mg)	Treatment duration (months)	Cardiac findings
Bogazzi et al.[55]	2008	100	100	279	67	No relevant findings
Colao et al.[56]	2008	50	50	414	74	Increased prevalence of moderate tricuspid regurgitation
Vallette et al.[126]	2008	70	70	282	55	No relevant findings
Devin et al.[127]	2008	45	0	NA	39	7% abnormalities
Lancellotti et al.[128]	2008	102	51	204	79	Significant increase in mitral tenting area
Kars et al.[129]	2008	47	78	363	62	Increased prevalence of mild tricuspid regurgitation; more mitral and aortic calcification and tricuspid thickening
Wakil et al.[130]	2008	44	566	311	45	Increased prevalence of mild tricuspid and pulmonic regurgitation
Herring et al.[131]	2009	50	50	443	79	No relevant findings
Nachtigall et al.[132]	2009	100	100	253	48	Mild increase in tricuspid regurgitation in female patients
Lafeber et al.[133]*	2010	115	115	227	115	No relevant findings
Tan et al.[134]	2010	72	72	126	53	No relevant findings

*This study included 19 patients with a diagnosis of acromegaly. Abbreviation: NA, not available.
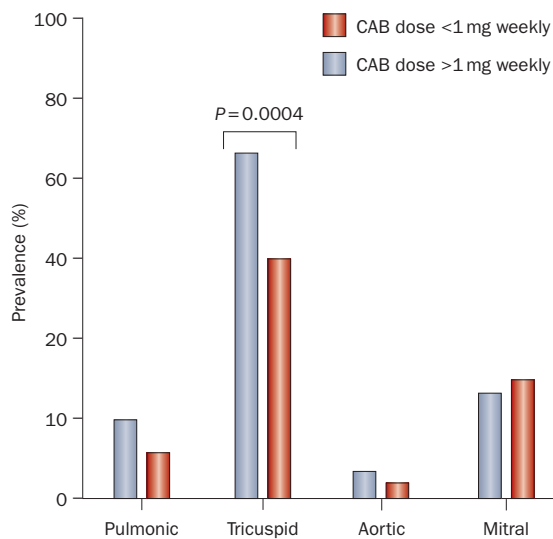

Figure 2 | Prevalence of valve regurgitation in patients with hyperprolactinemia treated with cabergoline for a median period of 74 months. The P value is derived from a Chi square analysis comparing prevalence of valve regurgitation in 22 patients treated with cabergoline at doses ≤1 mg weekly with 28 patients treated with higher doses. Figure is based on data from Colao and colleagues.[55] Abbreviation: CAB, cabergoline.

cabergoline dosages (Figure 2).[55] Subsequently, several systematic reviews[56–59] that included different studies showing abnormalities in valve physiology did not support the existence of an association between the long-term treatment of prolactinoma with cabergoline and clinically relevant valvular regurgitation. Nonetheless, the investigators conclude that data published thus far are inconclusive. Other studies, preferably prospective and on large series of patients who are followed up by echocardiography over a long-term period, are needed before any conclusion on the detrimental effect of cabergoline on cardiac valve disease in patients with prolactinomas can be drawn.

Additionally, only limited data are available on bromocriptine, which apparently has no effect on cardiac valve disease in patients with hyperprolactinemia.[59] Conversely, in patients with Parkinson disease, bromocriptine treatment is associated with a similar risk of cardiac valve disease as pergolide, with a clear dose-dependent effect.[60] No detrimental effects on cardiac valve disease are expected with quinagolide, as this drug is a non-ergot derivate, although no data are currently available.[61] Importantly, withdrawal of cabergoline or pergolide therapy has been associated with improvement or no further deterioration of cardiac valve disease.[62,63] An important contribution to this discussion has been published by Gu and coworkers,[64] who determined a bias in reading echocardiograms. In light of this finding, the studies showing detrimental effects of cabergoline on cardiac valve disease should be reanalyzed with a more careful study design and participating cardiologists blinded to the identity of patients or controls.

Dopamine agonist withdrawal

In the past, termination of dopamine agonist therapy has by and large resulted in a greater incidence of recurrent hyperprolactinemia compared with that observed after surgery.[18,26,65–76] As shown in Table 2, most patients showed recurrence of hyperprolactinemia after treatment withdrawal compared with 6.3–50.0% of those surgically treated for microprolactinomas.[6]

Table 2 | Dopamine agonist withdrawal

Reference	Number of patients				Drug	Treatment duration (months)	Normal prolactin (%)	Follow-up duration (months)
	Total	Micro	Macro	NTH				
Johnston et al.[65]	37	NA	NA	19	BRC	12–72	5.4	0.5
Zarate et al.[66]	16	NA	NA	0	BRC	Mean 24	37.5	24
Moriondo et al.[67]	36	36	0	0	BRC	Mean 12	22.0	Up to 30
Johnston et al.[68]	13 2	5 1	6 1	2 0	BRC PER	Mean 44 24	7.7 0	1.0–12.5 2
Maxson et al.[69]	7	7	0	0	BRC	>12	0	2
Wang et al.[70]	24	15	4	5	BRC	Mean 24	21.0	12–48
Winkelmann et al.[71]	40	NA	NA	NA	BRC	NA	18.4	5–25
Rasmussen et al.[72]	75	NA	NA	NA	BRC	Mean 24	44.0	>6
Van't Verlaat et al.[73]	12	0	12	0	BRC	Median 60	8.3	12
Ferrari et al.[74]	65	42	7	15	CAB	Median 14	31.3 (year 1) 66.7 (year 2)	3–24
Muratori et al.[75]	26	26	0	0	CAB	12	19.0	38–60
Cannavò et al.[76]	37	26	11	0	CAB	24	13.5	12
Di Sarno et al.[26]	39 39	23 23	16 16	0 0	CV CAB	12 12	0 10.2	0.5–2 12
Passos et al.[18]	131	62	69	0	BRC	Mean 47	20.6	Mean 44
Colao et al.[77]	200	105	70	25	CAB	>24	68.5	24–60
Biswas et al.[78]	22 67	22 67	0 0	0 0	BRC CAB	Median 36 Median 36	50.0 31.3	>12 >12
Colao et al.[80]	227	27	115	79	CAB	>24	58.6	24–96
Kharlip et al.[79]	46	31	11	4	CAB	52	46.0	2–48
Huda et al.[81]	40	40	0	0	DA	Mean 108	22.5	>12

Abbreviations: BRC, bromocriptine; CAB, cabergoline; CV, quinagolide; DA, dopamine agonists; Macro, macroadenoma; Micro, microadenoma; NA, not applicable; NTH, nontumoral hyperprolactinemia, PER, pergolide. Permission obtained from The Endocrine Society © Gillam et al. Endocr. Rev. **27**, 485–534 (2006).

Criteria for drug withdrawal

Previous studies have some limitations in the small series of patients assessed and lack of criteria for treatment withdrawal (Box 1). In 2003, a group of 200 patients with hyperprolactinemia underwent cabergoline withdrawal following a stringent protocol.[77] In this study, prolactin levels were normal after withdrawal of cabergoline for a maximum period of 5 years in >60% of patients, independent of tumor size at baseline.[77] After 5 years of drug withdrawal, the Kaplan–Meier estimator of recurrence of hyperprolactinemia was 24.0%, 32.6% and 43.3% in patients with nontumoral hyperprolactinemia, those with microprolactinomas and those with macroprolactinomas, respectively.[77] Interestingly, despite recurrence of hyperprolactinemia, no evidence of tumor regrowth was found in any patient, as documented by serial MRI.[77] Symptoms of gonadal dysfunction recurred in only 10 women (22.2%) and seven men (38.9%).[77] The maximal tumor diameter during cabergoline treatment was the most effective predictor of persistent hyperprolactinemia after drug withdrawal. Each additional mm of maximal tumor diameter, as measured on MRI before treatment withdrawal, increased the risk of recurrence of hyperprolactinemia by 19%.[77] Taking these results into consideration, dopamine agonist withdrawal

could be performed in order to spare patients from unnecessary treatment, particularly in individuals with no remnant tumor visible during treatment. One limitation of these results is the use of very strict selection criteria that apply only to a subset of patients with prolactinoma (Box 1). Accordingly, only 56% of the entire patient population with hyperprolactinemia would be eligible to undergo cabergoline withdrawal.

In another retrospective study, Biswas et al.[78] reported a prevalence of normalized prolactin levels after bromocriptine or cabergoline withdrawal of 31% and 50%, respectively (Table 2). Furthermore, all patients with remnant macroprolactinomas at treatment withdrawal, as well as 70% of those with remaining microprolactinomas, had recurrence of hyperprolactinemia after 96 months, suggesting that only patients with a negative MRI scan may undergo treatment withdrawal.[6] Kharlip et al.[79] found an overall recurrence of 54%, a rate higher than that observed in our series;[77] 52% of 31 patients with microprolactinoma, 55% of 11 patients with macroprolactinoma and 75% of four patients with nontumoral hyperprolactinemia had recurrence within 2–48 months of cabergoline withdrawal. The researchers confirmed that size of tumor remnant before drug withdrawal predicted recurrence and that none of the

- Serum prolactin levels in the normal range (<1,087 pmol/l, equal to 25 µg/l, in women and <652 pmol/l, equal to 15 µg/l, in men) during treatment with cabergoline (minimal treatment duration: 2 years)

- No remnant tumor visible on MRI or a reduction in tumor size by ≥50% compared with baseline size during treatment with cabergoline (minimal treatment duration: 2 years)

- In case of tumor persistence, patients are considered for withdrawal of cabergoline only if the outer border of the tumor is ≥5 mm or more from the optic chiasm, without evidence of invasion of one or both cavernous sinuses or any other critical area

- To minimize the risk of errors in reading MRI scans, all patients continued to receive cabergoline therapy for 12 months after fulfilling the withdrawal criteria and before withdrawal of the medication (total minimal treatment duration: 3 years before withdrawal)

- Patients were required to continue follow-up after withdrawal for at least 24 months
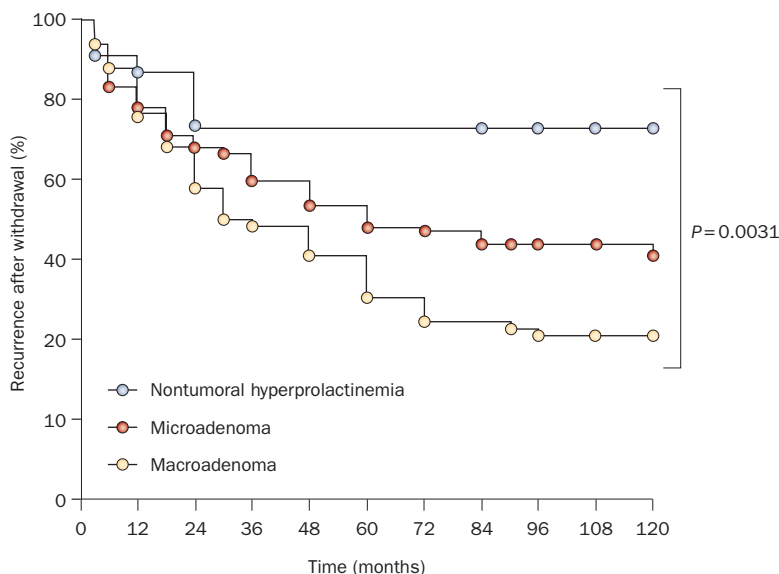

Figure 3 | Kaplan-Meier estimation of recurrence of hyperprolactinemia after 10 years of cabergoline withdrawal. The study population consisted of 27 patients with nontumoral hyperprolactinemia, 115 with microprolactinomas and 79 with macroprolactinomas.[80] Significance was obtained using the log-rank Manter–Cox test. Adapted with permission obtained from John Wiley and Sons © Colao, A. *et al. Clin. Endocrinol. (Oxf.)* **67**, 426–433 (2007).

tumors enlarged in the patients experiencing recurrence. Moreover, Kharlip *et al.*[79] showed that 28% of patients had symptoms of hypogonadism after drug withdrawal.

The major differences between our study[77] and the one by Kharlip *et al.*[79] are the number of patients analyzed, which was four times larger in our study, the use of cabergoline alone in our study, and methods adopted for withdrawal of cabergoline that occurred before study entry in the trial by Kharlip and colleagues. A subsequent analysis of our study population,[80] showed that normalized prolactin levels persisted, with no evidence of tumor regrowth, 24–96 months after cabergoline withdrawal in most patients with nontumoral hyperprolactinemia and microprolactinomas and in approximately 50% of those with macroprolactinomas. A nadir prolactin level

of <235 pmol/l, equal to 5.4 µg/l, and a maximal tumor diameter of 3.1 mm at the time of cabergoline withdrawal successfully predicted remission of hyperprolactinemia in 80% of patients.[80]

The latest analysis of this patient series (Figure 3), 10 years after cabergoline withdrawal, showed that 78% of patients with nontumoral hyperprolactinemia maintained normal prolactin levels during follow-up. Of the patients with microprolactinoma or macroprolactinoma, only 51% and 34%, respectively, had normoprolactinemia (Figure 3). In analogy with our previous data,[77] and with results reported by Kharlip *et al.*[79] and Huda *et al.*,[81] prolactin levels at the last follow-up examination or at diagnosis of recurrence of hyperprolactinemia correlated with the nadir prolactin level during treatment (Figure 4a), with the nadir tumor volume before withdrawal (Figure 4b) and with the duration of cabergoline treatment (Figure 4c). In the near future, we will complete the analysis of a large series of patients undergoing cabergoline withdrawal with a follow-up of 10 years in order to compare our results with those obtained after surgery.

Spontaneous remission

Pregnancy[82] and menopause[83] are conditions associated with spontaneous remission of hyperprolactinemia; however, neither was associated with an increased prevalence of normalized prolactin levels after cabergoline withdrawal.[77] Remission of hyperprolactinemia has also been reported in untreated patients. In particular, spontaneous remission was noticed in 32–55% of patients with microprolactinomas.[84–87] However, although disease regression might occur in one-third of patients with microprolactinomas or nontumoral hyperprolactinemia according to the natural disease history, this event is less likely to occur in patients with macroprolactinomas, and, thus, regression is more probable with previous cabergoline treatment.

Persistent remission

According to Dekkers *et al.*,[88] the proportion of patients who achieve normoprolactinemia in the long term after dopamine agonist withdrawal is 21%. A stratified analysis showed more frequent persistence of normal prolactin levels after treatment withdrawal in patients with idiopathic hyperprolactinemia (32%, 95% CI 5–80%) than in those with microprolactinomas (21%, 95% CI 10–37%) or macroprolactinomas (16%, 95% CI 6–36%). Factors associated with treatment success were the length of treatment duration and the use of cabergoline, albeit the latter factor did not achive statistical significance. In conclusion, withdrawal of cabergoline can be performed in patients who achieve normoprolactinemia and complete tumor disappearance, as determined by MRI, after at least 2 years of treatment, to avoid unnecessary overtreatment.[89] Patients should be followed up very strictly during the first year after withdrawal, as recurrence of hyperprolactinemia is highest during this time. Patients with macroadenomas require closer monitoring for recurrent hyperprolactinemia and tumor regression than others, as tumor regrowth may compromise vision.[77]

Figure 4 | Correlation analysis of data obtained by 227 patients included in the study by Colao and colleagues.[80] Prolactin levels at last follow-up examination or on recurrence of hyperprolactinemia compared with **a** | nadir prolactin levels before cabergoline withdrawal; **b** | nadir tumor diameter before cabergoline withdrawal and **c** | duration of cabergoline treatment before its withdrawal.


Aggressive prolactinomas

Aggressive pituitary tumors are classically defined as atypical pituitary tumors with extensive invasion of surrounding anatomical structures and/or rapid growth and/or giant size. The presence of subcranial, brain or systemic metastases is diagnostic of pituitary carcinoma.[90,91] In a neurosurgical series, aggressive pituitary tumors were found in 15% of all resected tumors, of which 11% were prolactinomas.[92] Aggressive pituitary tumors are notoriously difficult to manage owing to their size, invasiveness, speed of growth and high frequency of recurrence. In general, aggressive pituitary tumors are associated with poor prognosis, as therapeutic options are limited.[90,91] In the case of prolactinomas, atypical, aggressive tumors are found more frequently in men than women.[3,34,92–94]

More often than not, atypical prolactinomas are macroadenomas with invasion to structures surrounding the pituitary gland, as visible on MRI.[92] However, the prolactinoma is not the most frequent histotype of atypical pituitary adenomas, as reported by Zada and colleagues.[92] Of 121 patients who underwent transsphenoidal surgery, two patients with macroprolactinomas were diagnosed as having an atypical pituitary tumor; one of these two patients was found to be resistant to dopamine agonists.

Hystological characteristics

Standard histology and electron microscopy are normally unable to distinguish benign from aggressive, atypical invasive adenomas, which exhibit more malignant behavior, with a variable degree of nuclear atypia and cellular pleomorphism.[90,91] The 2004 WHO classification defines atypical pituitary adenomas as: an MIB-1 proliferation index >3%, excessive p53 immunoreactivity and increased mitotic activity.[92] However, a distinction between progressive and/or metastatic lesions and benign adenomas by analyzing mitotic indices, which are consistently higher in the former, is not always easy, as no particular threshold exists. Of all different biological markers associated with invasive potential of pituitary adenomas, the percentage of cells in the S phase of the cell cycle, which represents the proliferation rate, is particularly important.[93] The Ki-67 index, which can be obtained using the MIB-1 antibody, correlates best with tumor invasiveness and potentially with prognosis,[95] as Ki-67 labeling is increased in malignant and invasive tumors compared with benign adenomas (11.9% versus 4.7% versus 1.4%, respectively).[93] Additionally, prognostic value is also attributed to p53 expression, which is analyzed in a semiquantitative way by immunohistochemistry. However, presence or
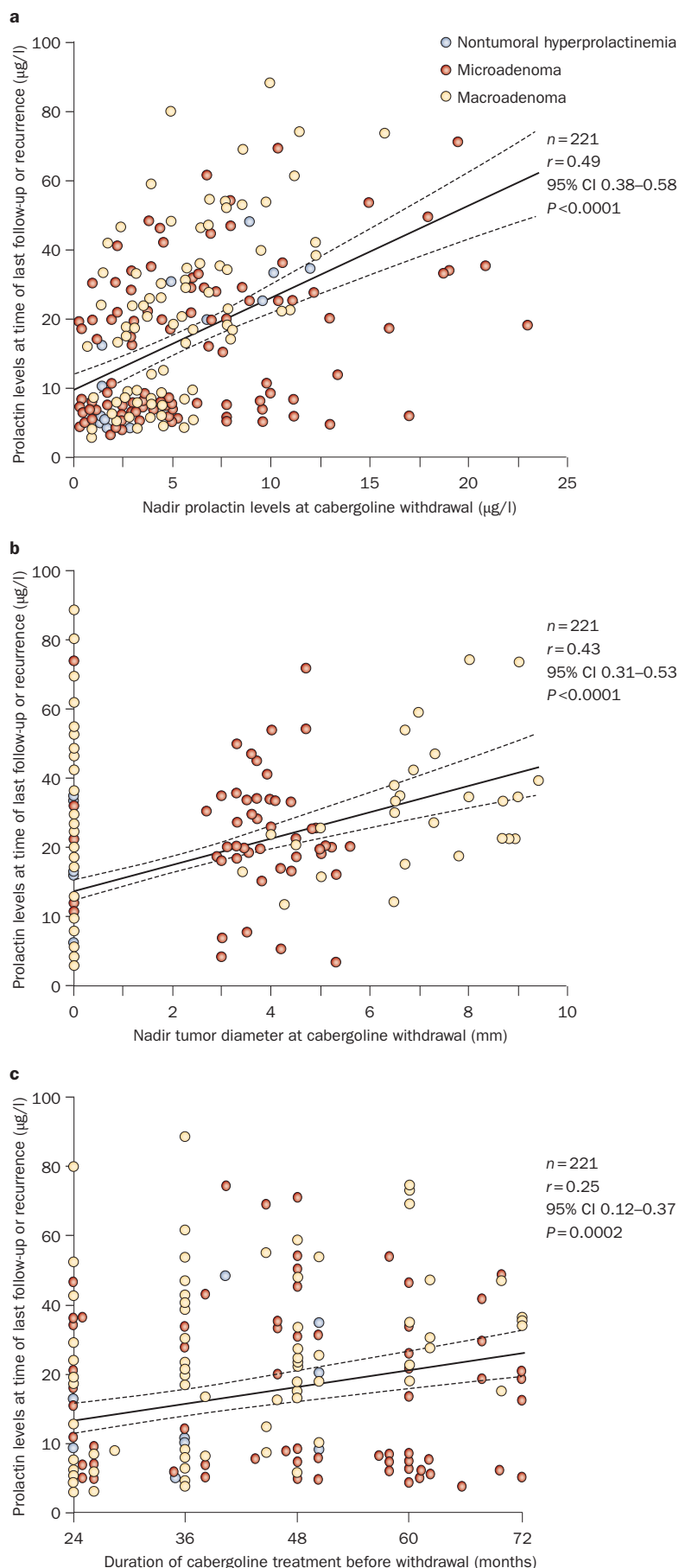
absence of p53 immunostaining is more indicative than the actual degree of staining to indicate aggressive and particularly malignant behavior.[96] Immunostaining of p53 in combination with an increased Ki-67 index may have a higher predictive value than either method alone.[90] Additionally, the microvascular density, indicated as a marker of angiogenesis, is also associated with metastatic potential and is considered to possess an independent role as predictor of patient survival.[97] A distinction between benign and aggressive, invasive or malignant tumors based on microvascular density is unclear, although pituitary carcinomas have a higher microvascular density than benign tumors. Moreover, microvascular density did not show any correlation with Ki-67 labeling.[97]

Of all the other markers investigated to differentiate benign from atypical tumors—including matrix metalloproteinase activity, cyclins and inhibitors of the cell cycle, markers of apoptosis and/or chromosomal gains and losses—a variable relevance has been found in several pituitary tumor types, with none of the mentioned pathways demonstrating a particular role in the differential diagnosis.[91]

Resistance to dopamine agonists

A minority of patients with hyperprolactinemia do not achive biochemical control of prolactin excess and/or do not have a reduction in tumor mass during treatment with dopamine agonists.[6] A comprehensive definition of dopamine agonist resistance is still lacking. Several proposals have been provided in the literature, such as failure to normalize prolactin levels, failure to reduce prolactin levels sufficiently to achieve ovulation or to 50% of baseline levels, or failure to reduce tumor mass during treatment with elevated dosages of these drugs.[6,98] Prevalence of resistance to dopamine agonists, in particular to the most used dopamine agonist cabergoline, is low, and reported in 10% of patients with microprolactinomas and 18% of those with macroprolactinomas.[17] Evidently, the number of patients defined as drug resistant depends on the administered dose. In our experience, we did not find beneficial effects in increasing dosage of cabergoline over 3.5 mg per week, but other investigators have suggested to increase the drug stepwise until a decrease of prolactin levels is observed.[35,98] Resistance was reported to be more common in patients with tumor extension into the cavernous sinuses,[34] and generally, atypical prolactinomas extend over the pituitary fossa.[92] Dopamine agonist resistance is a complex phenomenon owing to several abnormalities of the D_2 receptor,[98] both in quantitative expression and affinity to the ligand, so that targeting this receptor subtype is not followed by prolactin suppression and tumor shrinkage. A more detailed description of resistance to dopamine agonists is reported elsewhere.[6]

Late resistance

A particular condition that represents a negative prognostic factor in patients with prolactinomas is the occurrence of late resistance.[99] Patients who initially demonstrate a successful response to dopamine agonist therapy but develop a delayed resistance should be treated aggressively, as this phenomenon might be associated with malignant transformation of the prolactinoma.[99–101] One patient, who deceased because of a malignant prolactinoma characterized by late resistance, developed abnormal expression of guanine nucleotide-binding protein $G_s\alpha$ during the late stage, showing a phenotype of a mixed GH–prolactin-secreting tumor.[102]

Increasing dopamine agonist dosage

A patient who does not achieve control of prolactin levels generally receives an increased dosage of cabergoline.[98] Ono et al.[35] found that this drug normalized prolactin levels in all but one patient (0.7%). The rate of prolactin normalization increased from 34.6% to 73.1% and 88.5% when the dosage of cabergoline was raised from 3 mg per week to 6 mg and 9 mg weekly, respectively, finally reaching 96.2% at the highest dose of 12 mg per week.[35] Di Sarno et al.[17] determined that 10 of 56 patients (17.9%) with macroadenomas and six of 60 patients (10%) with microadenomas required increased doses of cabergoline. The maximal dose administered to drug-resistant patients was 7 mg weekly; however, normoprolactinemia was not achieved in any of the drug-resistant patients with this dosage.[17]

Delgrange et al.[36] reported prolactin normalization in 115 out of 122 patients (94%), with most patients (83%) achieving control with a dose of ≤1.5 mg cabergoline per week. Increase of the cabergoline dose higher than 1.5 mg weekly induced control of prolactin levels in 19 of 26 poor responders and nonresponders and, in analogy with Di Sarno et al.,[17] the investigators did not achieve a higher success rate when increasing the dosage up to 3.5 mg per week. In a single case report, use of extremely elevated doses of cabergoline in combination with testosterone and aromatase inhibitor therapy was successful in controlling both prolactin levels and the associated hypogonadism.[103] This study indicates that when testosterone replacement is required in male patients with prolactinoma, a negative influence of estrogen status on the prolactin-inhibitory effect cannot be completely ruled out.

Experimental treatments
Somatostatin analogues

Several experimental treatments used in selected case reports or in experimental settings have not yet been included in routine clinical practice. In summary, somatostatin analogues are widely used for the treatment of GH-secreting pituitary adenomas and neuroendocrine tumors[104] but not for prolactinomas. Somatostatin analogue therapy is successful in patients with acromegaly and neuroendocrine tumors because of a high density of somatostatin receptor subtype 2 (SSTR2) and SSTR5 on the cell surface of these tumors. Although somatostatin suppresses prolactin secretion in vitro in cultured prolactinomas,[105] neither somatostatin nor octreotide are able to inhibit prolactin levels in patients with prolactinomas.[106,107] Owing to a relative abundance of SSTR5,

rather than of SSTR2, in prolactinomas,[108,109] the novel compound pasireotide, which is characterized by a high affinity for SSTR1, SSTR3 and SSTR5, is expected to be able to treat some prolactinomas resistant to dopamine agonists in the near future. In primary cultures from both mixed GH-prolactin secreting adenomas and pure prolactin-secreting adenomas, Hofland et al.[109] have demonstrated a greater potency of pasireotide than octreotide in suppressing prolactin secretion.

Hybrid molecules

Some chimeric compounds that contain structural elements of both somatostatin and dopamine in a single molecule have been developed. These hybrid molecules possess a potent and selective agonist activity for both SSTR2 and the D_2 receptor. Their clinical use is based on the evidence that SSTR2 and D_2 receptor heterodimerize in the presence of appropriate ligands, thereby inducing the formation of a hybrid receptor showing enhanced inhibitory activity of adenyl cyclase.[110] BIM23A387, a chimeric somatostatin–dopamine molecule, was shown to strongly suppress prolactin secretion in vitro.[111,112] No data are yet available in patients with pituitary tumors using this drug. Although trials with this drug have been discontinued, a new chimera with identical in vitro results to BIM23A387 is under development.

Selective estrogen receptor modulators

Other treatment modalities address estrogen secretion and/or function because of known effects of this hormone on stimulation of prolactin secretion and proliferation of pituitary lactotrophs both in vitro and in vivo.[113] The discordant findings reported in studies on selective estrogen receptor modulators are potentially owing to use of different dosages, duration of treatment and behavior or characterstics of individual tumors.[6] Fulvestrant, a new estrogen receptor antagonist without agonist activity, decreased prolactin levels by 88% and attenuated tumor growth by 41% in rats with subcutaneous sommato-lactotroph tumors.[114] Treatment with tamoxifen for 5 days in eight patients with giant invasive prolactinomas, only mildly inhibited prolactin secretion.[115] Neither raloxifene nor fulvestrant have been tested in vivo in humans with prolactinomas.

Prolactin-receptor antagonists

Prolactin-receptor antagonists might constitute another possible treatment approach as these agents could block the proliferative effects of autocrine-derived prolactin, thereby improving the clinical consequences of persistently elevated prolactin levels.[116] However, the effects of prolactin-receptor antagonists are still not proven, both in normal and adenomatous human lactotrophs.

Temozolomide

Special attention has been given to temozolomide, an alkylating chemotherapeutic drug, indicated for treatment of glioblastoma,[117] as some efficacy of this drug has also been found in patients with neuroendocrine tumors[118] and in some with aggressive pituitary tumors

or carcinomas.[119] The efficacy of temozolomide seems to depend on the expression of the DNA repair protein MGMT.[120] As described by Raverot et al.,[119] eight patients, five with pituitary carcinomas (three prolactin-secreting and two ACTH-secreting) and three patients with aggressive pituitary tumors (one prolactin-secreting and two ACTH-secreting), received 4–24 cycles of orally administered temozolomide. Three patients responded to temozolomide, demonstrated by appreciable tumor shrinkage and reduced hormone secretion. MGMT expression did not predict tumoral response to temozolomide, because it was positive in one responder and negative in two nonresponders. Toxicity remained mild in all patients. Tumoral and/or hormonal response to temozolomide treatment has always been observed soon after treatment initiation in responder patients, and the absence of response after three cycles of treatment consistently predicted resistance to this treatment.[119] Unfortunately, initial response to temozolomide treatment is not always associated with long-term control, as a few cases showed tumor regression within 5–6 months after treatment initiation.[121,122]

Gene therapy

Gene therapy might represent a future option to treat aggressive pituitary adenomas but presently is still at an early stage of investigation.[6] The available approaches include gene-directed enzyme therapy, in which the gene encoding thymidine kinase is delivered to tumoral cells, together with systemic administration of a nucleoside analogue, such as ganciclovir. The nucleoside analogue is subsequently locally transformed into an active cytotoxin by thymidine kinase. When prolactinomas are targeted, expression of the gene encoding thymidine kinase is driven by the human prolactin (or cytomegalovirus) promoter.[123–125]

Conclusions

Nowadays, medical therapy with dopamine agonists is considered the gold standard of treatment in the vast majority of patients with prolactinomas, given its broad success in terms of control of prolactin excess and tumor shrinkage associated with minimal morbidity. The safety issue of cardiac valve disease following cabergoline therapy in patients with prolactinomas still requires some investigation. However, preliminary results seem to reassure that low doses of this drug, as used in patients with prolactinomas, are not detrimental for the cardiovascular system. Moreover, medical therapy seems not to be necessary throughout life; in some cases (20–60% in different series with varying follow-up and treatment), the dopamine agonist can be withdrawn without a recurrence of hyperprolactinemia or regrowth of prolactinomas. Only a small proportion of patients with hyperprolactinemia (10% in cabergoline-treated cohorts, 20% in bromocriptine-treated cohorts) do not respond successfully to dopamine agonists. Absence of prolactin control and of tumor shrinkage indicates resistance to these drugs, which represents a challenging condition because of poor response to nonmedical

approaches, including transsphenoidal surgery and radiotherapy. Investigations are currently focusing on new treatment options but presently, however, resistance to dopamine agonist remains a difficult-to-treat condition, and tumor progression to malignancy is possible. As a result, patients with tumors resistant to dopamine agonists deserve particular attention and careful follow-up.

Review criteria

A search for original articles published between 2006 and 2010 and focusing on pituitary adenomas was performed in MEDLINE and PubMed. The search terms used were "prolactin", "prolactinomas", "withdrawal", "cabergoline" and "valve disease". All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further papers.

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Author contributions