Cabergoline should be attempted in progressing non-functioning pituitary macroadenoma

Yona Greenman¹ and Marcello D Bronstein²

¹Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv-Sourasky Medical Center and Tel Aviv University, Tel Aviv, Israel and ²Neuroendocrine Unit, Division of Endocrinology and Metabolism, Hospital das Clinicas, University of Sao Paulo Medical School, Sao Paulo, SP, Brazil

Correspondence
should be addressed
to Y Greenman

Email
yonagr@tlvmc.gov.il

Abstract

Non-functioning pituitary adenomas (NFPA) usually present with symptoms of mass effect. Thus, the first-line treatment generally consists of transsphenoidal surgery. Since these tumors are usually large and invasive, post-surgical tumor remnants are common. Active surveillance is the follow-up strategy adopted by most pituitary centers, although the prevalence of residual tumor growth may reach 50% in 5–10 years, often leading to repeat surgery, radiation therapy, or both. NFPA remain the only pituitary tumor type for which no medical therapy has been approved. In this debate, we consider the evidence in favor and against using cabergoline to treat progressing NFPA.

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Introduction

Non-functioning pituitary adenomas (NFPA) are characterized by the absence of clinical or biochemical evidence of tumor-related hormone excess. They represent 15–37% of pituitary adenomas, with a calculated prevalence of 13.4–25.2 per 100 000 persons (1). The most common type (75–80%) of NFPA is of gonadotroph cell origin. Gonadotroph tumors are the only type of pituitary adenoma for which the majority are silent; very rarely, a clinical syndrome is caused by gonadotroph secretion and gonadal stimulation (2). In addition to staining for the transcription factor nuclear receptor subfamily 5 group A member 1 (NR5A1) these tumors generally show positive immunolabeling for β -FSH, β -LH, and α -subunit (3). Silent corticotroph tumors account for 15% of NFPA; about one-third of them stain positive only to the transcription factor T-box transcription factor 19 (TBX19), and not to ACTH. Tumors of the POU class 1 homeobox 1 (POU1F1) lineage account for 9% of NFPA and may be silent somatotroph,

lactotroph, or thyrotroph tumors. Null cell tumors, which do not stain for any of the lineage-specific pituitary transcription factors and hormones, are rare and account for about 2% of NFPA (4).

NFPA usually present with symptoms secondary to mass effect on surrounding tissues, including headaches, visual dysfunction, cranial nerve palsy, and hypopituitarism (5). In this context, surgery is the treatment of choice, as it rapidly achieves decompression and symptom amelioration (6, 7, 8). Most non-functioning pituitary macroadenomas are invasive; thus, full resection is often challenging and is achieved in 60–73% of patients, at most (9). Consequently, postoperative residual tumors are frequent, but their management is still a matter of debate. Here we present arguments for and against the treatment of growing NFPA remnants with cabergoline. The primary medical treatment of enlarging NFPA will not be discussed in view of the lack of research in this context.

For (Yona Greenman)

The clinical problem

Whereas in the past, most patients with postoperative NFPA remnants were treated with radiotherapy, the current prevalent approach is conservative monitoring. This is based on evidence that radiation therapy may be associated with significant long-term complications (10) and on the slow growth of most NFPA. The latter implies that tumor progression subsequent to surgery may not have adverse consequences that necessitate additional treatment. The main problems with the expectant approach are that tumor progression after surgery is not rare (11), and that additional surgery and radiotherapy are often required (12).

A meta-analysis reported a 12% recurrence rate for patients without detectable tumor after surgery; 46% of patients with postoperative remnants experienced disease progression, with a mean tumor volume doubling time of 3.4 years (13). A higher progression rate was reported for residual tumors with extrasellar extension (52.3–66.7%) than for remnants confined to the sella (30–33.3%) (14, 15).

Tampourlou and co-workers addressed the important issue of clinical outcomes of patients with tumor progression after primary surgical intervention. They identified 237 such patients from an original cohort of 765 (31%) (12). For the first regrowth, 141 patients (59.7%) were treated with additional surgery and/or radiotherapy, while 40.3% continued to be monitored. Of the latter, 34.8% eventually underwent reintervention with surgery, radiotherapy, or a combination of both. The 5-year second regrowth rate was 35.3%; one-third of these had undergone surgery for the first regrowth, and two-thirds were being followed conservatively. Of these 90 patients, 50 required additional surgery and/or radiotherapy. Four patients underwent additional surgery after a third regrowth. In a multivariate analysis, the main risk factor for a second regrowth was the type of management offered for the first regrowth, with hazard ratios (HR) of 0.43 (95% CI 0.238–0.901) for surgery and 0.098 (95% CI 0.045–0.212) for radiotherapy compared with monitoring alone. Of the 237 patients whose tumor progressed after initial surgery, 195 underwent reintervention with surgery and/or radiotherapy. This illustrates the implications of a 'wait and see' approach. Although major surgical complications are infrequent, they are not negligible and include new-onset hypopituitarism, cerebrospinal fluid leak, meningitis, cranial nerve injury, and visual compromise; a mortality rate of 0.3–0.5% has been reported (16). Conventional

and stereotactic radiotherapy are successful in prolonging progression-free survival but entail significant side effects, including long-term hypopituitarism and possible neurologic complications (17). Therefore, a medical treatment effective in preventing tumor progression and obviating the need for additional invasive therapies would be of great value.

Who should be treated?

Clinical guidelines have not been established for the postoperative management of NFPA. Extreme variability has been demonstrated in tumor volume doubling time and in growth kinetics. The latter may be characterized by an exponential or logistic growth model, or present with initial exponential growth followed by deceleration of growth (18). Distinguishing tumors that require close attention and earlier treatment from those with an indolent nature that can be followed conservatively is of utmost importance. Several molecular markers were explored as potential biomarkers. Epigenetic modifications including methylation of tumor suppressor genes and histone acetylation of growth factor genes have been implicated in aggressive behavior, tumor size, and disease progression (19). Reduced expression of the lncRNA MEG3 mediated by promoter hypermethylation has been associated with an invasive phenotype of NFPA (20), and overexpression of several circRNAs has been implicated in tumor progression, invasiveness, and recurrence of NFPA (21). Despite the considerable progress in this field, translation of the knowledge to the clinical setting still requires additional validation. An elevated Ki-67 proliferative index is recognized as an indication of tumor aggressiveness but has a low negative predictive value for recurrence (22). The histological type is a factor to consider; for example, silent corticotroph adenomas usually exhibit more aggressive biological behavior than gonadotropinomas. In addition, a large preoperative tumor size with cavernous sinus invasion, a large residual tumor with extrasellar extension, and young age are all factors that have been shown to confer greater risk for postoperative tumor growth (23) and that should be taken into account in the management of NFPA.

Treatment of NFPA with dopamine agonists

NFPA remain the only pituitary tumor subtype for which no medications have been approved. Most NFPA express dopamine receptors, predominantly dopamine receptor 2

(D2R) (24). Dopamine agonists (DA) reduce gonadotropin secretion and inhibit thymidine incorporation *in vitro* (25), providing a potential therapeutic target for NFPA. Modest size reduction in a minority of tumors was reported in early clinical studies using bromocriptine (5), but later studies using cabergoline were more encouraging (Table 1). One of the initial management challenges was identifying the cabergoline dose required for effectively controlling tumor growth. Different groups have used doses ranging from 1 to 3.5 mg/week (Table 1). In the absence of serum biomarkers to guide the treatment, the dose employed in the studies conducted by our group was chosen empirically. Considering the lower D2R expression levels in NFPA compared with prolactinomas (24), we assumed that the cabergoline dose required to treat the former would probably be higher than the mean dose used to treat the latter. Further, the mean cabergoline dose reported to be effective for the treatment of GH- and ACTH-secreting tumors, that also have lower D2R expression than prolactinomas but in which the dose could be titrated based on hormone measurements, was between 2.5 and 3 mg/week (26, 27, 28). Finally, because of safety concerns,

we elected to use an intermediate dose of 2 mg/week, which has not been associated with an increased risk of cardiac valvulopathy (29). The question of whether a lower dose could be similarly effective remains unanswered.

Primary prevention

Most of the available data concerning medical treatment of NFPA with DA pertains to primary prevention of tumor growth for patients in whom a residual mass was detected in the postoperative MRI (Table 1).

We conducted the largest study that has been published of DA for the treatment of NFPA in patients with residual tumors after surgery (30). Seventy-nine patients, followed for 8.8 ± 6.5 years, were treated with cabergoline (mean weekly dose 1.5 ± 0.7 mg), either subsequent to detection of a tumor remnant in the first postoperative MRI ($n = 55$) or after tumor growth became evident during conservative follow-up ($n = 24$). Tumor control was achieved in 87% of those treated in the early postoperative period, (tumor shrinkage in 38% and tumor stabilization in 49% of the patients), but only 47% of the tumors in the control group

Table 1 Studies of cabergoline treatment of NFPA.

Ref.	Year of study	Patients, <i>n</i>	F/U, months	Dose, mg/week	Shrinkage	Stable	Growth	Strengths	Limitations
(33)	2001	13	12	1	7	5	1		Small cohort, uncontrolled, short F/U
(58)	2004	9	12	3	5	1	3	D2R analysis	Small cohort, uncontrolled, short F/U
(34)	2013	19	6	2	6	9	4		Small cohort, uncontrolled, short F/U
(59)	2015	9	6	3	6	3	0	D2R analysis	Small cohort, uncontrolled, short F/U
(30)	2016							Large cohort, long F/U, controlled D2R analysis	Not randomized, MRI criterion for size changes
		PP: 55 SP: 24 CON: 60	105 $\pm$ 78	1.5 $\pm$ 0.7	21 7 0	27 7 28	7 10 32		
(3)	2019							Large cohort, randomized controlled study, D2R analysis	MRI interpretation issues, relatively short F/U
		59 CON: 57	24	3.5	17 6	39 42	3 9		
Total		PP: 164 CON: 117			62 (37.8%) 6 (0.05%)	84 (51.2%) 70 (59.8%)	18 (11%) 41 (35%)		

CON, control; D2R, dopamine receptor 2; F/U, follow-up; PP, primary prevention; SP, secondary prevention.

remained stable during follow-up ($n=60$, $P < 0.0001$). The relative and absolute risk reduction for tumor growth were 76 and 40.6% respectively, with a number needed to treat (NNT) of 2.46. Importantly, DA treatment led to a significant decrease in the need for additional invasive therapies: only 13% of patients who received preventive DA treatment required additional surgery or radiotherapy, compared to 42% in the control group ($P = 0.0008$).

A single-center open-label randomized clinical trial assessed the utility of cabergoline vs nonintervention in 116 patients with NFPA who had residual tumor after transsphenoidal surgery. At the end of 2 years, for the treatment ($n=59$) and the nonintervention ($n=57$) groups, tumor size decreased in 29 and 10.5% of patients, respectively and enlarged in 5 and 16% ($P=0.01$). The tumor growth-free rates were 23.2 and 20.8 months in the treatment and nonintervention groups, respectively ($P=0.01$) (31).

Although an association between the (qualitative) expression of the D2R short isoform with response to DA has been suggested, tumor response to DA treatment was not found to be related to D2R protein or mRNA expression in tumor tissue, as examined by immunohistochemistry (IHC) (30, 31) and quantitative real time-PCR (30). This suggests that additional factors may mediate the growth inhibitory effects of DA.

No reliable factors are known that may predict the clinical response of NFPA to medical therapy with DA. In contrast with the decrease in expression levels of D2R in resistant prolactinomas, no such correlation has been found in NFPA. Further, no serum biomarkers are available to guide the treatment. Whereas the medical treatment of secreting tumors is based on measuring circulating hormone levels, this important follow-up tool is lacking in NFPA (32), and the appraisal of treatment effectiveness relies on periodic MRI. In view of the slow-growing nature of many of these tumors, several years may be needed to determine treatment effectiveness. In this scenario, one could argue that patients with indolent tumors may be treated unnecessarily and that DA therapy should, therefore, not be offered to all patients with residual tumors after surgery. Indeed, patients with no or with minimal tumor remnant after surgery, with a low probability of recurrence or tumor progression, should be followed conservatively. On the other hand, in my opinion, DA treatment should be offered to patients presenting with large tumors and cavernous sinus invasion; patients with large remnants after surgery, particularly if extrasellar and patients with a high probability for tumor progression.

Secondary prevention

Less information is available regarding the efficacy of DA treatment for secondary prevention in patients who already experienced tumor growth. The papers by Lohman *et al.* (33) and Garcia *et al.* (34) included patients with residual or recurrent tumors, but treatment outcomes are given for the group as a whole. In the seminal paper by Van Schaardenburg *et al.* (35), in the year prior to initiation of treatment with bromocriptine, there was radiological evidence for tumor progression in five patients whereas the residual tumor was stable in six subjects. In three of the five patients with progression, there was tumor reduction, and in the remaining two, no further growth occurred under DA treatment during a follow-up time of 40 and 55 months (35). In our study using bromocriptine, tumor progression was halted in 6 and tumor shrinkage occurred in 2 of 13 patients in whom there was evidence for tumor progression before treatment initiation, with an overall control rate of 61.5% (36). In our more recent study, 14 of 24 patients (58.4%) who had evidence of tumor enlargement during conservative follow-up were controlled by treatment with cabergoline (tumor shrinkage in seven and restraint of tumor growth in seven) (30).

Regarding the specific focus of this debate, namely, the use of cabergoline in tumors found to be progressing in MRI, one should take into account the individual patient's characteristics, as in any clinical decision process in medicine. Thus, a tumor slowly growing into the sphenoid sinus of an elderly patient, that probably would not necessitate additional surgery in the future, may not require medical intervention. On the other hand, I would recommend treatment for patients with large growing remnants, particularly those with suprasellar extension, which, if left untreated, would most probably require additional surgery or radiation therapy (30). Shrinkage or restraint of tumor progression when there is already evidence of active tumor growth can be clearly detected within the initial 6–12 months of treatment, such that the need for further intervention can be considered within a safe time frame.

We have not observed tumor shrinkage leading to complete resolution of the adenoma. On the other hand, responders in whom treatment was discontinued by the patient or following recommendations given by other professionals have experienced tumor regrowth and progression. The optimal duration of treatment has not been defined, and further studies are needed to address this important point.

Most studies included only patients with 'null tumors' or those with positive staining for gonadotropins, such that the recommendations based on the published data cannot be extended to silent corticotropinomas or the other rarer silent tumors. Because staining for transcription factors was not performed, one cannot rule out the possibility that some of the 'null tumors' were TBX19 positive, ACTH negative tumors.

Safety issues

Cardiac valve abnormalities, as seen in patients who receive high dosages of DA for Parkinson's disease, are a concern, particularly in prolonged treatment periods. A meta-analysis of 13 studies found an association between treatment with low-dose cabergoline and an increased prevalence of tricuspid regurgitation on echocardiographic surveillance (37). However, a recent large population-based analysis failed to detect an association of cabergoline treatment for prolactinoma with clinically significant valvulopathy (38). Hence, cabergoline doses of up to 2 mg/week, as used for the treatment of NFPA, seem safe in this regard.

DA-induced impulse control disorders (pathological gambling, hypersexuality, punding, compulsive shopping, and compulsive eating) have been identified in up to 17% of individuals with prolactinoma under medical treatment (39). DA therapy has also been temporally associated with severe depression, manic episodes, and psychosis, regardless of prior psychiatric history (40). Although these are serious side effects, they are completely reversible after cessation of treatment. Hence, adequate patient orientation regarding the possibility of such complications, together with clear instructions to interrupt treatment if they occur, can ensure treatment safety.

Conclusions

Cabergoline can effectively restrain growth or induce tumor shrinkage in almost 60% of already progressing NFPA and has been shown to reduce the need for additional surgery and radiotherapy, with their potential associated complications. In view of the lack of alternative medical therapies, I consider a therapeutic trial with cabergoline valid and worthwhile for progressing non-functioning pituitary macroadenomas.

Against (Marcello D Bronstein)

The basis for the treatment of NFPA with dopamine agonists

The rationale for the medical treatment of NFPA has a clinical and translational basis. Clinically, an alternative to surgery and radiotherapy is needed for residual/recurrent tumors. Translationally, the concept of ligand/receptor activity is a rational justification for such an approach. Accordingly, the presence of dopamine D2 receptors in NFPA may lead to the use of DA drugs for such purpose.

Indeed, *in vitro* studies indicate that the dopaminergic system is an important agent of NFPA growth arrest. For instance, Gagliano *et al.* (41) demonstrated that the DA cabergoline reduces cell viability in NFPA via inhibition of vascular endothelial growth factor (VEGF). Nevertheless, the findings of that study strongly suggest that cabergoline effects are mediated by D2R. This notion is reinforced by the evidence of increased VEGF concentration and VEGF mRNA expression in the pituitaries of female D2R knockout compared to WT mice (42). Renner *et al.* (43) investigated the heterogenous dopamine D2R subtype messenger RNA expression in NFPA. They assessed growth inhibitory action of the DA bromocriptine, evidenced by haloperidol-reversible suppression of [3H]thymidine incorporation. Growth inhibitory action of bromocriptine was detected in one adenoma in which only the mRNA of the D2 short isoform was expressed and in two adenomas with a predominant or an equal expression of D2 short vs D2 long receptor subtype. In adenomas in which the D2 long isoform was the only or the predominant isoform, growth suppression after application of bromocriptine was not observed. This suggests that the presence of the D2 short isoform in the adenomas favors the growth-suppressive response to bromocriptine. Moreover, another *in vitro* study reached the conclusion that DA receptors expressed by NFPA induce a defective transduction pathway that does not involve inhibition of cAMP production. This led to the notion that DA drugs probably act as a poor inhibitory agent for this pituitary tumor subtype (44).

Dopamine agonists for the treatment of functioning pituitary adenomas

In the clinical realm of pituitary tumors, bromocriptine was the first DA drug to become commercially available; excellent results have been demonstrated for prolactin normalization and tumor shrinkage in prolactinomas (45).

Cabergoline, a DA with a high affinity for the D2R, was shown to be associated with better tolerability, easier administration, and higher efficacy than bromocriptine. Therefore it became the gold standard for the treatment of prolactinomas (46). The presence and density of D2R in prolactinomas correlated with the response to DA, mainly the D2R short isoform; D2R was significantly less expressed in prolactinomas resistant to DA therapy (47, 48, 49).

D2R expression has also been detected in GH- and ACTH-secreting tumors (50, 51), and indeed a number of studies showed that DA, especially cabergoline, caused clinical and hormonal improvement in patients with acromegaly and Cushing's disease (26, 27, 28).

Appraisal of DA treatment effectiveness in NFPA

In secreting tumors, the effectiveness of cabergoline therapy can be assessed by GH/IGF-1 and ACTH/cortisol assays, thus precluding the continuation of ineffective treatment. A major concern regarding the treatment of NFPA with DA is the absence of a reliable hormonal marker to evaluate treatment outcome, as in secreting pituitary tumors. The alpha subunit is not always elevated in NFPA (52), and some conditions such as menopause can mislead the results. Nevertheless, even without a reliable marker, DA has been administered for NFPA since the 1980s. A chronological analysis of clinical studies targeting this issue will be described henceforth. In the analysis of these studies, one should bear in mind that spontaneous tumor reduction may occur as the natural history of NFPA. Along this line, in 34 (11%) of 304 patients with nontreated NFPA macroadenomas, compiled from 10 series, a decrease in tumor size was observed (53). Yavropoulou *et al.* (54) recently reviewed 10 studies that described the natural history of untreated NFPA; two of which were not included in the review by Dekkers *et al.* (53). This series reported a spontaneous decrease in tumor volume in 0–30% of NF-macroadenomas.

The clinical experience: bromocriptine

Regarding bromocriptine, small series showed conflicting results, mostly indicating ineffectiveness in tumor reduction. Wollesen *et al.* (55) described tumor shrinkage in 9 of 11 NFPA patients under a huge dose of bromocriptine (15–60 mg/day). Nevertheless, patients were either treatment-naïve or with a history of surgery or radiotherapy, therefore compromising the results. In another short-term (6 weeks) pre-surgical trial with bromocriptine, 7.5 mg/day, tumor size did not decrease in any of six patients

with NFPA (56). In 19 of 20 patients treated with chronic bromocriptine (7.5–20 mg/day for 1–32 months) (57), no changes in NFPA size were documented by CT during the treatment; visual defects worsened in four patients. The authors concluded that bromocriptine treatment, at least at the doses capable of shrinking macroprolactinomas, seems to be of limited value in patients with NFPA.

Possible explanations for the poor results of studies with first-generation DA are its lower affinity for the D2R compared with cabergoline, heterogeneity of dose and time of treatment, and methodological factors. The latter include small population sizes, the lack of randomized / placebo-controlled studies, and the assessment of tumor dimensions by CT scan rather than the more accurate MRI. Subsequently, studies with more efficacious and better tolerated cabergoline emerged.

The clinical experience: cabergoline

In a study of nine patients with post-surgical residual NFPA, administered cabergoline (58), the initial dose of 1 mg/week in the first month was extended to 3 mg/week for 11 additional months. Significant improvement in visual fields after 1 year of treatment was observed in four of five (80%) patients with a baseline visual field defect. Significant tumor shrinkage occurred in five of nine (56%) patients at the end of the study and was prominent in two of them. On the other hand, non-significant tumor shrinkage was observed in one patient, and a slight increase in tumor size was seen in the remaining three patients. Notably, all the tumors that demonstrated significant shrinkage were associated with D2 expression. All but one of the tumors without significant shrinkage did not express the D2 receptor. Expression of the D2 short isoform was associated with a higher degree of tumor reduction. The major weight of this study concerns the association between tumor shrinkage and D2R expression, particularly the D2 short isoform. Nevertheless, some flaws in the methodology can impair the interpretation of the results. These include the small cohort and the short-term follow-up.

Greenman *et al.* (36) addressed the issue of DA administration for patients with NFPA in a larger cohort. They assessed outcomes of 33 post-surgical patients: 20 with remnant tumors, treated preventively (group I); 13 with tumor growth during follow-up (group II). All the patients were initially treated with bromocriptine (mean dose 8 ± 0.7 mg/day), but 10 subjects were switched to quinagolide (up to 300 mg/day) or cabergoline (up to 1.5 mg/week) due to side effects. The control group consisted of 47 patients who only underwent surgery. The actuarial

tumor growth-free survival rates at 2 years were 94 and 50% in treatment groups I and II, respectively. For the control group, the actuarial tumor growth-free survival rates at 2 and 5 years were 65 and 17%, respectively. Although this study apparently indicates the efficacy of DA in the management of post-surgical tumor growth in patients harboring NFPA, certain flaws may compromise its interpretation and validation. For one, although the authors considered the treated and control groups as matched, the patients were treated in different departments; the Ki-67 expression was not cited, and the degree of cavernous sinus invasion was not detailed. Secondly, the type and dose of the DA drugs administered were characterized by considerable heterogeneity. Thirdly, the actuarial tumor growth-free survival in the DA groups referred to only 2 years of follow-up. Fourthly, differences between the control group and treatment group II were not significant, therefore, the distinctive tumor behavior in the two treatment groups could explain the different outcomes. Last, but not least, D2R expression in the tumors was not assessed.

Vieira Neto *et al.* (59), albeit with a small cohort of 23 patients, shed some light on DA treatment for NFPA. They compared nine patients with residual tumors treated with a fixed dose of cabergoline (3 mg/week) for 6 months. Notably, 14 patients refused such an approach. Six of the nine patients responded to treatment with significant tumor shrinkage, according to the three-dimensional method of tumor volume evaluation on MRI. All six exhibited D2R protein tumor expression, scored as 2 by IHC. Of the three patients without tumor reduction, the IHC score for D2R was 1 for one patient, and the receptor expression was not available for the remaining two patients. This study showed homogeneity regarding cabergoline doses and imaging evaluation and importantly, indicated the association of D2R expression with tumor response to the DA treatment. However, some aspects of the study may weaken the analysis of the results. First, the lack of DR2 expression data in two of three nonresponding patients precluded reaching a conclusion regarding DR2 protein expression and its hypothetical role as a predictor of tumor response. Secondly, tumor invasiveness and Ki-67 immunoexpression were not compared between responders and non-responders. Thirdly, silent GH, ACTH, prolactin, and thyroid-stimulating hormone (TSH)-secreting tumors were excluded from the study, to increase homogeneity, and only null cell and gonadotroph NFPA were included. However, even null cell tumors, when submitted to transcription factor evaluation, may be classified as silent plurihormonal Pit-1-positive tumors (previously called

‘silent subtype 3 adenomas’). These tumors usually exhibit more aggressive biological behavior (60, 61, 62).

Subsequently, Greenman *et al.* (30) assessed postoperative NFPA management, namely DA therapy and conservative follow-up, in a larger cohort of patients. Seventy-nine patients were followed for 8.8 ± 6.5 years while treated with DA (bromocriptine up to 10 mg/day or cabergoline up to 2 mg/week), initiated upon residual tumor detection on postoperative MRI (preventive treatment (PT) group, $n = 55$), or when tumor growth was detected during follow-up (remedial treatment (RT) group, $n = 24$). The control group ($n = 60$), from another pituitary referral center, did not receive DA. The authors reported that tumors decreased, remained stable, or enlarged in 38, 49, and 13%, respectively, of patients in the PT group, and in 0, 53, and 47% of the control group. The 15-year progression-free survival rates were 0.805, 0.24, and 0.04, for the PT, RT and control groups, respectively, $P < 0.001$. Additional surgery or radiotherapy was indicated for 42% of the patients in the control group, compared to 38% and 13% in the RT and PT groups, respectively ($P = 0.002$). Of note, outcome events were not related to NFPA D2R expression. Although the cohort was relatively large, the study had several limitations. First, drug type and dose were highly variable among the patients. Secondly, a variation of 2 mm in tumor size was considered significant. An error of method should be considered, especially due to the inclusion of patients from different referral centers. Also, regarding MRI, though the invasion of the cavernous sinus has been quantified as over grade 2 in the Knosp classification, the Knosp 2 does not necessarily imply invasion. Therefore, a more precise classification of invasion is needed, as an important aspect of tumor aggressiveness. Thirdly, regarding IHC, null cell tumors may represent silent plurihormonal tumors, with more aggressive behavior. Finally, the unexpected absence of a correlation between tumor behavior and D2R expression is relevant to the interpretation of the results.

More recently, Batista *et al.* (31) performed a randomized, parallel, open-label clinical trial that compared cabergoline with nonintervention in a large cohort of patients (cabergoline group: $n = 59$; control group: $n = 57$) with residual NFPA over 2 years after transsphenoidal surgery. The dose of cabergoline was fixed as 3.5 mg/week, and MRI tumor volume was evaluated by the Di Chiro and Nelson formula. D2R was evaluated by the histo (H)-score method. Residual tumor volume shrinkage ($<25\%$), stabilization and enlargement ($\geq 25\%$) were observed in 28.8, 66.1 and 5.1% of patients, respectively, in the medical therapy group, and in 10.5, 73.7 and 15.8%

of patients, respectively, in the control group ($P=0.01$). Progression-free survival rates were 23.2 and 20.8 months for the study and control groups, respectively ($P=0.01$). Of note, D2R immunoexpression (performed in only 79 tumors) did not differ between the cabergoline and control groups.

Although this was the best designed study published to date, a number of limitations should be considered in interpreting the results. First, the follow-up of the study was relatively short. Secondly, as discussed by the authors, the Di Chiro and Nelson mathematical equation formula to estimate the residual tumor volume is fallible, as the shape of the residual tumor can mislead the assessment. Additionally, differences in cavernous sinus invasion between the two groups were not mentioned. Thirdly, tumor stabilization was similar between the groups. Additionally, tumor shrinkage occurred mostly in the first year and could be ascribed to the natural history of operated NFPA. Fourthly, three patients with PRL-silent adenomas subjected to cabergoline were included in this protocol. Interestingly, one of them presented strong tumor shrinkage (35%). As prolactin levels were not mentioned, prolactinomas cannot be ruled out. Fifthly, as mentioned above, null cell adenomas could represent the more aggressive silent plurihormonal tumors. Finally, the expected correlation of D2R immunoexpression with residual tumor behavior was not found, thus compromising the interpretation of the results.

Conclusions

Though an efficacious medical therapy for NFPA is highly expected and desired, in my opinion, the use of DA drugs needs more data to be considered an option to conservative surveillance, radiotherapy, or reoperation. The influence of the natural history of residual post-surgical NFPA should be considered. Additionally, complications of such treatment as impulsive control disorders and valvar heart disease should not be underestimated, mainly with higher doses of cabergoline.

Concluding remarks

Despite several caveats concerning design, length of follow-up and assessment results, studies have consistently shown the effectiveness of cabergoline in controlling NFPA remnant growth in a considerable proportion of patients. However, more data are needed to control the possibility of spontaneous tumor shrinkage or stability

independent of DA treatment. As cabergoline is a generic drug, a commercial incentive is lacking to conduct a large, randomized, placebo-controlled trial with long follow-up that could then verify the current data.

In the larger studies on NFPA, the lack of correlation between D2R expression and the clinical response to DA is puzzling. Nevertheless, the absence of a pathophysiological explanation for the therapeutic effect does not negate its presence or detract from its value.

Accounting for the lack of alternative medical therapies and the potential complications related to repeat surgeries and radiation therapy, we agree that a therapeutical trial with cabergoline can be considered for progressing non-functioning pituitary macroadenomas based on the present evidence.

Declaration of interest

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

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