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Resistance to Cabergoline as Compared with Bromocriptine in Hyperprolactinemia: Prevalence, Clinical Definition, and Therapeutic Strategy

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To evaluate the prevalence of resistance to cabergoline treatment, we studied 120 consecutive *de novo* patients (56 macroadenoma, 60 microadenoma, 4 nontumoral hyperprolactinemia) treated with cabergoline (CAB) compared with 87 consecutive *de novo* patients (28 macroadenoma, 44 microadenoma, 15 nontumoral hyperprolactinemia) treated with bromocriptine (BRC) for 24 months. Resistance was evaluated as inability to normalize serum PRL levels (first end point) and to induce tumor shrinkage (second end point).

After 24 months, PRL normalization and tumor shrinkage after CAB and BRC treatments, respectively, were obtained in 82.1% and 46.4% of macroprolactinomas ($P < 0.001$) and in 90% *vs.* 56.8% of microprolactinomas ($P < 0.001$). The median doses of CAB and BRC able to fulfill the two criteria of treatment success were 1 mg/wk and 7.5 mg/d in macroprolactinomas, 1 mg/wk and 5 mg/d in microprolactinomas, and 0.5 mg/wk and 3.75 mg/d in nontumoral hyperprolactinemia. Hyperprolactinemia persisted in 17.8% of macroprolactinomas, 10% of microprolactinomas, and after CAB at doses of 5–7 mg/wk and in 53.6% of macroprolactinomas, 43.2% of microprolactinomas, and 20% of nontumoral hyperprolactinemic patients, after BRC at doses of 15–20 mg/d. In these resistant macro- and microprolactinomas, the maximal tumor diameter was reduced by 43.7 ± 3.6% and 22.1 ± 3.7% and by 59.3 ± 7.1% and 4.3 ± 2.1% after CAB and BRC, respectively ($P < 0.001$).

In conclusion, long-term CAB treatment induced the successful control of hyperprolactinemia associated with tumor shrinkage in a higher proportion of patients than did BRC treatment. In a small number of patients (*i.e.* 17.8% of macroprolactinomas and 10% of microprolactinomas), however, CAB treatment did not normalize serum PRL levels despite reducing tumor mass, even at very high doses. Therefore, an absence of tumor shrinkage cannot be considered as end point to indicate resistance to CAB, and increasing the dose of CAB higher than 3 mg/wk does not seem to be helpful in controlling PRL hypersecretion. (*J Clin Endocrinol Metab* 86: 5256–5261, 2001)

CURRENTLY, THE TREATMENT with dopamine agonists (DAs) is the first therapeutic option in patients both with micro- and macroprolactinoma as well as in those with the so-called "nontumoral" or "idiopathic" hyperprolactinemia (1–3). DAs, particularly bromocriptine (BRC) and cabergoline (CAB), are highly effective in normalizing serum PRL levels, so restoring gonadal function in over 90% of cases (4–6). In addition, a clear-cut tumor mass shrinkage, even tumor disappearance at magnetic resonance imaging (MRI) scan, is reported in 70–80% of patients (7–10). A minority of patients, ranging from 10–20% in different series, however, does not achieve control of PRL hypersecretion and/or tumor shrinkage even after treatment with a variety of DAs at high doses (11–14). During DA treatment, further tumor growth has been reported in some of these poorly responsive patients (15).

The definition of therapy resistance to DAs is still a matter of controversy. The absence of serum PRL normalization and/or tumor shrinkage after at least 3 months of treatment with BRC at the dose of 15 mg daily defines resistant patients (16). Another definition considers a less than 50% reduction in serum PRL levels despite increasing the daily dose to at least 15 mg BRC daily (12). True resistance, however, can be only documented by molecular biology studies, demonstrating the absence or poor expression of D_2 receptors on the membrane surface of tumor cells, or abnormalities at a postreceptor level (12, 15). On a practical level, however, molecular biology studies cannot be routinely performed. On the other hand, the majority of resistant patients present partial, more than complete, therapy resistance, and progressive increase of the dose of BRC or CAB is generally able to induce normoprolactinemia. However, sometimes the dose of DAs cannot be increased due to tolerance-related problems: in this respect, CAB was recently shown to be superior to BRC (12, 13, 17).

The experience accumulated with CAB in treating hyperprolactinemia is still limited. In this retrospective study, we evaluated the prevalence of CAB resistance, in terms of PRL normalization and tumor shrinkage, in a large series of *de novo* patients compared with a similar group of consecutive *de novo* patients treated with BRC, used as controls.

Patients and Methods

Patients

From 1996 to 1998, 120 consecutive *de novo* patients with hyperprolactinemia (90 women and 30 men, aged 15–72 yr) were admitted to our Department and were included into this study after their informed

Abbreviations: BRC, Bromocriptine; CAB, cabergoline; CT, computed tomography; DA, dopamine agonist; MRI, magnetic resonance imaging.

consent had been obtained. Data of 25 patients with macroprolactinoma (12 and 13, respectively) have been previously reported (9, 10). As a control group, data were analyzed from 87 consecutive *de novo* patients with hyperprolactinemia (59 women and 28 men, aged 17–74 yr) treated with BRC as first choice therapy from 1988 to 1990. All 207 patients were followed at the Department of Molecular and Clinical Endocrinology and Oncology, "Federico II" University of Naples. Among the 120 and 87 CAB- and BRC-treated patients, 56 (46.7%) and 28 (32.2%) ($\chi^2 = 3.8$; $P = 0.051$) patients had a macroadenoma, 60 (50%) and 44 (50.6%) had a microadenoma, and 4 (3.3%) and 15 (17.2%) ($\chi^2 = 10.1$; $P < 0.001$) patients were classified as having nontumoral hyperprolactinemia. PRL levels at diagnosis in the different groups are shown in Table 1.

Hypopituitarism, apart from hypogonadism, was present in 16 (28.6%) and 13 (46.4%) patients with macroadenoma treated with CAB and BRC, respectively ($\chi^2 = 1.9$; $P = 0.1$). In particular, in the CAB group, three patients had GH deficiency, four had TSH deficiency, four had GH + ACTH deficiency, and five had GH, TSH + ACTH deficiency. In the BRC group, two patients with giant adenomas had panhypopituitarism, five had GH + TSH deficiency, and six had ACTH deficiency. All men had decreased libido and impaired sexual potency, whereas all women had menstrual disturbances; 76 women treated with CAB (84.4%) and 42 treated with BRC (71.2%) had spontaneous or expressible galactorrhea. Among patients with macroprolactinoma, 19 in the CAB group (34%) and 15 in the BRC group (53.6%) ($\chi^2 = 2.6$; $P = 0.1$) had visual field defects. Loss of libido was evaluated only in men because of difficulty in assessing this symptom in women.

Treatment protocol

In the 60 patients with microadenoma and 4 with nontumoral hyperprolactinemia, CAB treatment was administered orally at a starting dose of 0.25 mg once weekly for the first week, twice weekly during the second week, and then 0.5 mg twice weekly. After 2 months of treatment, dose adjustment was carried out every 2 months on the basis of serum PRL suppression. In the 56 patients with macroadenoma the starting CAB dose was 0.5 mg once a week for the first week, then twice weekly. Dose adjustment was performed as for patients bearing microadenomas or nontumoral hyperprolactinemia. In patients not normalizing PRL levels, the CAB dose was progressively increased to 5–7 mg/wk. In 85 of 87 patients, BRC was administered orally at the starting dose of 2.5 mg in the evening after dinner for 2 wk, then the dose was increased to 5 mg, 2.5 mg after lunch and dinner. In patients not normalizing PRL levels, the BRC dose was progressively increased to 15–20 mg/d. The remaining two patients had giant adenomas (>4 cm maximal diameter) and were treated at a starting BRC dose of 5 mg/d. Dose adjustment was performed as for patients not bearing giant adenomas. In patients achieving serum PRL levels below 5 μg/liter (the low normal range) the dose of CAB and BRC was reduced to maintain serum PRL levels into the normal range; thus, the final CAB dose ranged from 0.25–7 mg/wk and BRC dose ranged from 2.5–20 mg/d. All 207 patients were followed for at least 24 months.

Study protocol

The 29 patients with hypopituitarism received standard replacement therapy with L-thyroxine (50–100 μg orally daily), cortisone acetate (25–37.5 mg/d), and DDAVP (5–20 μg/d), where necessary. GH deficiency was not correct during the 2-yr study. Serum free thyroid hormones, urinary free cortisol, and serum and urinary $Na+$ and K^+ measurements periodically assessed adequacy of hormone replacement therapy. At study entry, the serum PRL level was calculated as the average value of a 6-h profile by blood sampling every 30 min (0800–1400 h). After 1, 3, 6, 12, 18, and 24 months of treatment, serum PRL levels were assayed at 0800, 0815, and 0830 h and the average value was taken for analysis. A general clinical examination and a simple questionnaire for the monitoring compliance (poor, moderate, satisfactory, and excellent) was performed every month for the first 3 months, and then quarterly throughout the follow-up.

Imaging studies

From 1996 to 1998 tumor mass was evaluated by MRI, as reported previously (13). MRI studies were performed on clinical 0.5T and 1T scanners, using T1-weighted gradient recalled-echo (repetition time, 200–300 min; echo time, 10–12 min; flip angle, 90 degrees; 4 signal averages) in the sagittal and coronal planes. In each measurement 7–11 slices were obtained, with a slice thickness of 2–3 mm and an in-plane spatial resolution of 0.7–0.97 mm (the matrix was 192–256 × 256 on a field of view of 24–25 cm on the sagittal plane, and 160–256 × 256 on a field of view of 18–20 cm in the coronal plane). The acquisitions were repeated before and after the administration of 0.1 mmol gadolinium chelate (diethylene-triamine pentacetate). From 1988 to 1990 tumor mass was evaluated by a third-generation high-resolution computed tomography (CT) scan with contrast enhancement. MRI and CT were performed before and after 3, 6, 12, and 24 months of treatment in macroprolactinomas and before and after 12, and 24 months in microprolactinomas. The maximal tumor diameter was calculated in all macro- and microadenomas and was expressed in mm. Tumor shrinkage was evaluated as reduction of the maximal tumor diameter compared with baseline in a semiquantitative way: less than 10% = absent; 11–20% = mild; 21–30% = moderate; more than 30% = remarkable.

Visual perimetry

In all patients with macroprolactinoma the assessment of visual field defects, by Goldmann-Friedmann perimetry, and visual acuity was performed at baseline. The ophthalmologic examination was repeated every

TABLE 1. Patients profile at study entry

	CAB treatment	BRC treatment	*P*
Total no.	120	87	0.051
W/M	90/30	59/28	0.327
Age median (yr)	29 (31.9 ± 1)	29 (32.8 ± 1.3)	0.9
Macroprolactinomas	56	28	0.051
W/M	29/27	9/19	0.141
Age median (yr)	33.5 (35.8 ± 1.9)	29 (31.7 ± 2)	0.5
Basal PRL levels (μg/liter)	2069 ± 415.1	1625 ± 241.9	0.5
Maximal tumor diameter (mm)	20.4 ± 1.5	22 ± 1.8	0.525
Patients with pituitary hormone deficiency (no.)	16	13	0.168
Patients with visual field defects (no.)	19	15	0.135
Microprolactinomas	60	44	0.953
W/M	57/3	35/9	0.033
Age median (yr)	27.5 (28.5 ± 0.9)	29.5 (33.7 ± 2)	0.4
Basal PRL levels (μg/liter)	114.1 ± 4.9	191 ± 9.6	<0.0001
Maximal tumor diameter (mm)	7.7 ± 0.2	6.7 ± 0.2	<0.0001
Nontumoral hyperprolactinemia	4	15	<0.0001
W/M	4/0	15/0	
Age median (yr)	28.5 (28.7 ± 0.5)	30 (32.7 ± 2.9)	0.4
Basal PRL levels (μg/liter)	67.5 ± 4.6	89.5 ± 4.4	0.025

Data are expressed as mean ± SEM.

3–6 months during the follow-up in the 34 patients with visual disturbances.

Assays

Serum PRL levels were assessed by RIA using commercial kits (Radim, Pomezia, Italy). The intra- and interassay coefficients of variation were 5% and 7%, respectively. The normal range was 5–25 μg/liter in women and 5–15 μg/liter in men.

Statistical analysis

Data are reported as mean ± SEM. The statistical analysis was performed by means of the SPSS, Inc. (Cary, NC) package using ANOVA. Statistical significance was set at 5%. *Post hoc* analysis was performed by means of paired and unpaired *t* tests applying Bonferroni's correction. In this case, the significance was set at 1%. The χ^2 test was also used where appropriate.

Results

First end point: PRL normalization

CAB treatment normalized serum PRL levels in 46 patients (82.1%) with macroprolactinoma, 54 patients (90%) with microprolactinoma, and in all 4 patients with nontumoral hyperprolactinemia within the first 6 months of treatment (Tables 2–4). Recovery of gonadal and sexual function was observed in all 46 (24 women) macroprolactinomas, 54 (51 women) microprolactinomas, and in all 4 women with nontumoral hyperprolactinemia. Galactorrhea disappeared in all 72 responsive women. The median CAB dose able to normalize PRL level was 1 mg/wk in macroprolactinomas, 1 mg/wk in microprolactinomas, and 0.5 mg/wk in nontumoral hyperprolactinemia (Tables 2–4). The remaining 10 patients (17.8%) with macroprolactinoma and 6 (10%) with microprolactinoma were treated with increasing doses of the drug, up to a maximum of 7 mg/wk, for at least 12 months. Recovery of gonadal and sexual function was obtained in 3 (women) of 10 macroprolactinomas and in all 6 (4 women) microprolactinomas. Galactorrhea disappeared in all four resistant women. At the 24-month follow-up, none of the 16 patients persistently normalized PRL levels, which were decreased by 88.5 ± 2.1% in macroprolactinomas and 49.8 ± 3.0% in microprolactinomas. In macro- and in microprolactinoma-resistant patients, the median CAB dose was 5 and 7 mg/wk, respectively. Responsive and resistant patients had similar age, basal PRL levels, and maximal tumor diameter at diagnosis (Tables 2 and 3).

BRC treatment normalized serum PRL levels in 13 patients (46.4%) with macroprolactinoma, 25 patients (56.8%) with microprolactinoma, and 12 patients (80%) with nontumoral hyperprolactinemia within the first 12 months (Tables 2–4). Recovery of gonadal and sexual function was obtained in 11 (4 women) of 13 macroprolactinomas, in all 25 (17 women) microprolactinomas, and in all 15 women with nontumoral hyperprolactinemia. Gonadal and sexual function were not normalized in the remaining two responsive men with giant adenomas. Galactorrhea disappeared in 40 responsive women. The median BRC dose was 7.5 mg/d in macroprolactinomas, 5 mg/d in microprolactinomas, and 3.75 mg/d in nontumoral hyperprolactinemia. The remaining 15 patients (53.6%) with macroprolactinoma, 19 (43.2%) with microprolactinoma, and 3 (20%) with nontumoral hyperprolactinemia were treated with increasing doses of the drug up to a maximum of 20 mg/d. Recovery of gonadal and sexual function was obtained in 13 (2 women) of 15 macroprolactinomas and in 19 (all women) with microprolactinomas resistant to BRC. Galactorrhea disappeared in all two resistant women. At the 24-month follow-up, none of the 37 patients stably normalized PRL levels, which were decreased by 86.1 ± 3.8% in macroprolactinomas, by 62.0 ± 2.5% in microprolactinomas, and by 62.7 ± 5.5% in nontumoral hyperprolactinemia. The median BRC dose in these patients was 17.5 mg/d in macroprolactinomas, 15 mg/d in microprolactinomas, and 15 mg/d in nontumoral hyperprolactinemia (Tables 2–4).

TABLE 2. Efficacy of a 24-month treatment with CAB and BRC in macroprolactinomas

	CAB treatment	BRC treatment	*P*
Total no.	56	28	0.051
W/M	29/27	9/19	0.141
Age median (yr)	33.5 (35.8 ± 1.9)	29 (31.7 ± 2)	0.4
No. patients with visual field defects	19	15	0.135
Responsive	46	13	0.002
Basal PRL levels (μg/liter)	2069 ± 415.1	1625 ± 241.9	0.5
Nadir PRL levels (μg/liter)	5.7 ± 0.7	8.8 ± 1.7	0.08
Dose median (range)	1 (0.5–1.5 mg/wk)	7.5 (2.5–10 mg/d)	
PRL decrease (%)	98.6 ± 0.2	98.9 ± 0.4	
Dose	1.1 ± 0.0 mg/wk	7.3 ± 0.6 mg/d	
Maximal tumor diameter (mm)	19.9 ± 1.5	17.8 ± 1.8	0.481
Nadir tumor diameter (mm)	7.4 ± 0.8	6.6 ± 1.3	0.630
Maximal tumor decrease (%)	62.2 ± 3.8	64.4 ± 5.2	0.775
Patients with recovered visual field defects (no.)	17	11	0.006
Resistant	10	15	0.002
Basal PRL levels (μg/liter)	2069 ± 415.1	1625 ± 241.9	0.5
Nadir PRL levels (μg/liter)	68.6 ± 7.2	217 ± 88.1	0.183
PRL decrease (%)	88.5 ± 2.1	86.8 ± 3.8	
Dose median	5 (5–7 mg/wk)	15 (15–30 mg/d)	
Dose	5.4 ± 0.3 mg/wk	17.7 ± 1.1 mg/d	
Maximal tumor diameter (mm)	23.6 ± 4.9	25.6 ± 2.8	0.705
Nadir tumor diameter (mm)	11.9 ± 1.5	19.7 ± 2.1	0.010
Maximal tumor decrease (%)	43.7 ± 3.6	22.2 ± 3.8	0.0007

Data are expressed as mean ± SEM.

TABLE 3. Efficacy of 24-month treatment with CAB and BRC in microprolactinomas

	CAB treatment	BRC treatment	*P*
Total no.	60	44	0.01
W/M	57/3	35/9	0.033
Age median (yr)	27.5 (28.5 ± 0.9)	29.5 (33.7 ± 2)	0.5
Responsive	54	25	<0.0001
Basal PRL levels (μg/liter)	114.1 ± 4.9	191 ± 9.6	<0.0001
Nadir PRL levels (μg/liter)	5.9 ± 0.6	9.1 ± 1.0	0.07
PRL decrease (%)	94.5 ± 0.6	94.4 ± 0.8	
Dose	0.8 ± 0.0 mg/wk	6.1 ± 0.2 mg/d	
Dose median (range)	1 (0.25–1.5 mg/wk)	5 (2.5–7.5 mg/d)	
Maximal tumor diameter (mm)	7.8 ± 0.2	6.4 ± 0.3	<0.0001
Nadir tumor diameter (mm)	3.1 ± 0.3	3 ± 0.6	0.885
Maximal tumor decrease (%)	58.9 ± 4.6	55.6 ± 8.1	0.712
Resistant	6	19	<0.0001
Basal PRL levels (μg/liter)	114.1 ± 4.9	191 ± 9.6	<0.0001
Nadir PRL levels (μg/liter)	60.2 ± 7.8	67.3 ± 5.6	0.5
PRL decrease (%)	49.8 ± 3	62 ± 2.5	
Dose	6.3 ± 0.4 mg/wk	17.5 ± 0.6 mg/d	
Dose median (range)	7 (5.7 mg/wk)	17.5 (15–20 mg/d)	
Maximal tumor diameter (mm)	7.8 ± 0.6	6.8 ± 0.4	0.194
Nadir tumor diameter (mm)	3.0 ± 0.5	6.4 ± 0.4	<0.0001
Maximal tumor decrease (%)	59.4 ± 7.2	4.3 ± 2.1	<0.0001

Data are expressed as mean ± SEM.

TABLE 4. Efficacy of 24-month treatment with CAB and BRC in patients with nontumoral hyperprolactinemia

	CAB treatment	BRC treatment	*P*
Total no.	4	15	<0.0001
Age median (yr)	28.5 (28.7 ± 0.5)	30 (32.7 ± 2.9)	0.30
Basal PRL levels (μg/liter)	67.5 ± 4.6	89.5 ± 4.4	0.025
Responsive	4	12	0.8
Basal PRL levels (μg/liter)	67.5 ± 4.6	85.3 ± 4.6	0.054
Nadir PRL levels (μg/liter)	1.6 ± 0.2	5.8 ± 1.0	0.043
Percent PRL decrease (%)	97.6	92.3	
Dose	0.6 ± 0.1 mg/wk	4.2 ± 0.6 mg/d	
Dose median (range)	0.5 (0.5 mg/wk)	3.7 (2.5–1 mg/d)	
Resistant	0	3	0.8
Basal PRL levels (μg/liter)	0	106.6 ± 6.3	
Nadir PRL levels (μg/liter)	0	39.5 ± 6.1	
PRL decrease (%)		62.8 ± 5.5	
Dose	0	15 ± 0.0 mg/d	
Dose median (range)	0	15 (15 mg/d)	

Data are expressed as mean ± SEM.

For the entire population, control of hyperprolactinemia was achieved in a higher proportion of patients after CAB (86.7%) than after BRC (57.5%) ($\chi^2 = 21.1$, $P < 0.0001$).

Second end point: tumor shrinkage

After 12 months of CAB treatment tumor shrinkage was achieved in 44 (95.6%) of 46 responsive patients with macroprolactinoma (Table 2) and in 48 (88.8%) of 54 responsive patients with microprolactinoma (Table 3). Tumor shrinkage was remarkable in 41 macroprolactinomas (89.1%) and 42 microprolactinomas (77.8%): tumor mass disappeared in 8 (17.4%) and 16 (29.6%) of them. The maximal tumor diameter was reduced by 62.2 ± 3.8% and 58.9 ± 4.6% in macro- and microprolactinomas, respectively. In the 16 resistant patients, tumor shrinkage was moderate in 1 and remarkable in 6; the maximal tumor diameter was reduced by 43.7 ± 3.6% and 59.4 ± 7.2% in macroprolactinomas and microprolactinomas, respectively (Table 2). Tumor mass did not disappear in any of these patients.

After 12 months of BRC treatment, tumor shrinkage was also achieved in all 13 responsive patients with macroprolactinoma (Table 2) and in 20 of 25 (80%) responsive patients with microprolactinoma (Table 3). Tumor shrinkage was remarkable in all 13 patients with macroprolactinoma and in 16 (64%) of those with microprolactinoma. The maximal tumor diameter was reduced by 64.4 ± 5.2% and 55.6 ± 8.1% in macroprolactinomas and in microprolactinomas, respectively (Tables 2 and 3). Tumor mass completely disappeared in 2 (7.8%) patients with macroprolactinoma and in 10 (40%) patients with microprolactinoma. In the 34 resistant patients, tumor shrinkage was moderate in 7 and remarkable in 5; the maximal tumor diameter volume was reduced by 22.2 ± 3.7% and 4.3 ± 2.1% in macroprolactinomas and microprolactinomas, respectively (Table 2). Tumor mass did not disappear in any of these patients.

The effect of CAB and BRC treatment on visual perimetry

Seventeen (89.5%) and 11 (73.3%) patients with visual field defects had normalization of visual perimetry after 12 months of treatment, after CAB or BRC, respectively. No

improvement and/or normalization of visual field defects was observed in the remaining patients throughout the study period.

Adverse effects

CAB and BRC treatments were well tolerated. Four (3.3%) CAB-treated patients and 19 (21.8%) BRC-treated patients had side effects that most commonly were nausea, postural hypotension, and drowsiness after the dose of 5 mg/wk CAB and 15 mg/d BRC, respectively. No patient was withdrawn from CAB nor from BRC treatment because of side effects.

Discussion

The results of the present retrospective study demonstrated that the treatment with CAB for 24 months resulted in PRL normalization and tumor shrinkage in a higher proportion of macroprolactinomas (82.1% *vs.* 46.4%) and microprolactinomas (90% *vs.* 56.8%) than after the treatment with BRC in a similar cohort of patients for an identical period of time. Treatment outcome was similar in patients with nontumoral hyperprolactinemia, but, interestingly, the prevalence of nontumoral hyperprolactinemia was higher in the cohort of patients studied at the beginning compared with those studied at the end of the decade of the 1990s: the higher sensitivity of MRI compared with the CT scan was likely responsible for the difference in the imaging-based diagnosis of these patients.

The two different study periods were selected on the basis of treatment approach to hyperprolactinemia. In fact, from 1990 to 1995 in Italy quinagolide was also available, and several patients received quinagolide as th efirst drug and were, thus, excluded. The current results are in agreement with several other studies reported in the last 5 yr demonstrating the efficacy of CAB treatment in hyperprolactinemia (7, 10, 17–20). In particular, the prevalence of therapeutic success obtained in our series was very similar to that reported by a multicenter retrospective study including records from 455 patients (21). However, the majority of the prior studies did not report a comparison with the standard treatment of hyperprolactinemia (*i.e.* BRC), which is still currently used in several countries as first-line therapy for hyperprolactinemia. In one of the earlier studies comparing the efficacy of CAB with that of BRC (19) in a group of 459 women with microprolactinoma and nontumoral hyperprolactinemia, it was shown that a 24-wk period of CAB treatment was more effective, both in terms of normalizing PRL levels (83% *vs.* 59%) and achieving ovulatory cycles or pregnancies (72% *vs.* 52%), and better tolerated than BRC (19). In this study, CAB was also shown to induce significantly less frequent, less severe, and shorter-lived side effects than BRC (19). In our study, the prevalence of side effects was very low after administration of both drugs, and none of the 207 patients was withdrawn from treatment because of side effects. When microprolactinomas and nontumoral hyperprolactinemic patients were considered together, in accordance with previous studies (18–19, 21), the results of the current one confirm the superior efficacy of CAB *vs.* BRC: 90.6% *vs.* 62.7%. Both by our group (9–10) and by others (7, 8, 20, 21), CAB was also shown to be highly effective in inducing tumor shrinkage in macroprolactinomas. The tumor shrinking effect of CAB was confirmed by the results of the current controlled study: all patients with macroprolactinoma, even those considered resistant, had reduction in the maximal tumor diameter.

This result is intriguing when facing the issue and the definition of therapy resistance. In fact, currently the definition of resistance to chronic therapy with DAs is based on the inability of a drug to induce PRL normalization and/or to cause tumor shrinkage after at least 3 months of therapy with increasing doses up at least to 15 mg/d, for BRC (12, 15). In no prior study were the two end points (PRL normalization and tumor size) considered separately. Taking into account the results of BRC treatment, indeed none of the patients with microprolactinoma who did not achieve PRL normalization had tumor shrinkage, leading to the concept that, at least in this subgroup of patients, the two end points can be considered together. However, both when analyzing the results of BRC treatment in macroprolactinomas and of CAB treatment in patients with macroprolactinoma or microprolactinoma, it appeared that patients not achieving PRL normalization actually had different degrees of tumor shrinkage. Furthermore, because the literature considers as resistant a patient who did not normalize hyperprolactinemia after treatment with 15 mg/d BRC, we calculated the median dose for both drugs in the attempt to suggest how high the dose should be before the clinical definition of resistance to CAB therapy could be satisfied. The median doses able to control hyperprolactinemia in macroprolactinoma-, microprolactinoma-, and nontumoral hyperprolactinemic-responsive patients were, respectively, 1.0, 1.0. and 0.5 mg/wk for CAB and 7.5, 5.0, and 2.5 mg/d for BRC. It is unclear why the dose of at least 15 mg/d BRC was chosen to define BRC therapy resistance (12, 15). Based on our findings, 15 mg/d BRC is a dose 2 times higher than the average dose used in macroprolactinomas, 3 times higher in microprolactinomas, and 6 times higher in nontumoral hyperprolactinemia. Using the same criteria, the dose of CAB sufficiently high to define a resistant patient should be 2.0 mg/wk in macroprolactinomas and 3.0 mg/week in microprolactinomas and nontumoral hyperprolactinemia. In this study, the maximal dose used in our 16 CAB-resistant patients was much higher: 5.0 mg/wk in macroprolactinoma and 7.0 mg/wk in microprolactinoma. The CAB dose was slightly higher in resistant microprolactinomas than in macroprolactinomas, because notable tumor shrinkage is achievable in macroprolactinomas and the risk of intratumoral hemorrhage is rather high with CAB, even when given at low doses (22). Interestingly, despite the evidence that PRL levels were further reduced by 88.5 $\pm$ 2.1% in macroprolactinomas and by 49.8 $\pm$ 3.0% in microprolactinomas after CAB dose increase, and despite the evidence of tumor shrinkage, none of these patients achieved complete therapeutic success, nor did they have tumor disappearance.

In conclusion, long-term CAB treatment induced the successful control of hyperprolactinemia associated with tumor shrinkage in a higher proportion of patients than did BRC treatment. In a small number of patients (*i.e.* 17.8% of macroprolactinomas and 10% of microprolactinomas), however, CAB treatment did not induce PRL normalization, despite

reducing tumor mass, even after very high dose administration. Increasing the dose of CAB higher than 3.0 mg/wk does not seem to be helpful in controlling PRL hypersecretion, and in patients with visual compromise surgical tumor removal is mandatory. Lastly, the absence of tumor shrinkage does not seem to be a helpful feature to classify resistance to CAB both in macroprolactinomas and in microprolactinomas.

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References

1. **Cunnah D, Besser GM** 1991 Management of prolactinomas. Clin Endocrinol (Oxf) 34:231–235
2. **Molitch ME, Thorner MO, Wilson C** 1997 Management of prolactinomas. J Clin Endocrinol Metab 82:996–1000
3. **Colao A, Annunziato L, Lombardi G** 1998 Treatment of prolactinomas. Ann Med 30:452–459
4. **Vance M, Evans W, Thorner M** 1984 Bromocriptine. Ann Intern Med 100: 78–91
5. **Webster J** 1996 A comparison review of the tolerability profiles of DA agonists in the treatment of hyperprolactinemia and inhibition of lactation. Drug Safety 14:228–238
6. **Bevan JS, Webster J, Burke CW** 1992 Dopamine agonists and pituitary tumor shrinkage. Endocr Rev 13:221–235
7. **Biller BMK, Molitch ME, Vance ML, et al.** 1996 Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline. J Clin Endocrinol Metab 81:2338–2343
8. **Ferrari C, Abs R, Bevan JS, et al.** 1997 Treatment of macroprolactinoma with cabergoline: a study of 85 patients. Clin Endocrinol (Oxf) 46:409–413
9. **Colao A, Di Sarno A, Landi ML, et al.** 1997 Long-term and low-dose treatment with cabergoline induces macroprolactinoma shrinkage. J Clin Endocrinol Metab 82:3574–3579
10. **Colao A, Di Sarno A, Landi ML, et al.** 2000 Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. J Clin Endocrinol Metab 85:2247–2252
11. **Delgrange E, Crabbe J, Donckier J** 1998 Late development of resistance to bromocriptine in a patient with macroprolactinoma. Horm Res 49:250–253
12. **Delgrange E, Maiter D, Donckier J** 1996 Effects of the dopamine agonist cabergoline in patients with prolactinoma intolerant or resistant to bromocriptine. Eur J Endocrinol 134:454–456
13. **Colao A, Di Sarno A, Sarnacchiaro F, et al.** 1997 Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. J Clin Endocrinol Metab 82:876–883
14. **Brue T, Pellegrini I, Gunz G, et al.** 1992 Effects of dopamine agonists CV 205–502 in human prolactinomas resistant to bromocriptine. J Clin Endocrinol Metab 74:577–584
15. **Brue T, Pellegrini I, Priou A, et al.** 1992 Prolactinomas and resistance to dopamine-agonists. Horm Res 38:84–89
16. **Kovacs K, Stefaneanu L, Hovarth E** 1995 Prolactin-producing pituitary tumor: resistance to dopamine agonist therapy. J Neurosurg 82:886–890
17. **Webster J, Piscitelli G, Polli A, et al.** 1993 The efficacy and tolerability of long-term cabergoline therapy in hyperprolactinemic disorders: an open, uncontrolled, multicentre study. Clin Endocrinol 39:323–329
18. **Ferrari C, Paracchi A, Mattei AM, et al.** 1992 Cabergoline in the long-term therapy of hyperprolactinemic disorders. Acta Endocrinol 126:489–494
19. **Webster J, Piscitelli G, Polli A, et al.** 1994 A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. N Engl J Med 331:904–909
20. **Cannavò S, Curtò L, Squadrito S, et al.** 1999 A first choice treatment in patients with previously untreated prolactin-secreting pituitary adenoma. J Endocrinol Invest 22:354–359
21. **Verhelst J, Abs R, Maiter D, et al.** 1999 Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. J Clin Endocrinol Metab 84:25518–2522
22. **Cappabianca P, Lodrini S, Felisati G, et al.** 2001 Cabergoline-induced CSF rhinorrhea in patients with macroprolactinoma. Report of three cases. J Endocrinol Invest 24:183–187