0021-972X/00/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 85, No. 6
Printed in U.S.A.

Macroprolactinoma Shrinkage during Cabergoline Treatment Is Greater in Naive Patients Than in Patients Pretreated with Other Dopamine Agonists: A Prospective Study in 110 Patients*

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ABSTRACT

To investigate whether previous treatment with bromocriptine (BRC) or quinagolide (CV) impairs a subsequent response to long-term cabergoline (CAB) treatment, we prospectively studied 110 patients with macroprolactinoma. Four groups of patients were considered: 1) naive: 26 untreated patients with a mean serum PRL levels of 1013.4 ± 277.7 μg/L (±SEM; range, 185.5–5611 μg/L); 2) intolerant: 19 patients previously shown to be intolerant of BRC treatment with a mean serum PRL level of 539.4 ± 172.2 μg/L (range, 174-3564 μg/L); 3) resistant: 37 patients shown to be resistant/hyporesponsive to BRC, CV, or both, with a mean serum PRL level of 602.6 ± 136.8 μg/L (range, 148-3511 μg/L); and 4) responsive: 28 patients previously treated with BRC or CV for 1–5 yr, achieving normoprolactinemia and restoration of gonadal function, but no longer treated with BRC or CV because of poor compliance or because the drug was not available. After a 15- to 30-day washout period, the serum PRL level was 397 ± 43.1 μg/L (140–978 μg/L). CAB treatment was given at doses ranging 0.25–3.5 mg weekly for 1 yr to 110 patients, for 2 yr to 104 patients, and for 3 yr to 81 patients. Magnetic resonance imaging was performed before and after 12, 24, and 36 months of CAB treatment to evaluate significant tumor shrinkage (>80% reduction of pretreatment tumor volume).

Among the 26 naive patients, normoprolactinemia was achieved in 21 (80.8%) after 1–6 months at 0.25–2 mg/week and in 5 patients after 24 months at 0.5–3 mg/week. Tumor volume was reduced from 1431.5 ± 310.3 to 47.2 ± 21.5 mm^3 ($P < 0.0001$); average tumor shrinkage was 92.1 ± 2.9%; significant tumor shrinkage was observed in 92.3% of patients, and tumor mass completely disappeared in 16 patients (61.5%).

Among the 19 intolerant patients, normoprolactinemia was achieved in 18 (94.7%) after 1–6 months of CAB treatment at 0.25–1 mg/week. One patient remained mildly hyperprolactinemic. Tumor volume was reduced from 1925 ± 423.1 to 842.0 ± 330.7 mm^3 ($P < 0.001$); average tumor shrinkage was 66.2 ± 6.4%; significant tumor shrinkage was obtained in 42.1% of patients, and tumor mass completely disappeared in 4 patients (21%).

Among the 37 resistant patients, normoprolactinemia was achieved in 19 (51.3%) after 6–12 months at 1–2 mg/week and in the remaining 18 patients after 18–24 months at 3–3.5 mg/week. Tumor volume was reduced from 1208.0 ± 173.7 to 471.2 ± 87.3 mm^3 ($P < 0.005$); average tumor shrinkage was 58.4 ± 4.9%; significant tumor shrinkage was obtained in 10 of 33 patients (30.3%), and in no patient did tumor mass completely disappear.

Among the 28 responsive patients, normoprolactinemia was achieved in 23 (82.1%) after 1–6 months at 1–2 mg/week and in 5 patients after 12 months at 3 mg/week. Tumor volume was reduced from 1351.3 ± 181.5 to 757.1 ± 193.6 mm^3 ($P < 0.01$); average tumor shrinkage was 59.2 ± 6.2%; significant tumor shrinkage was obtained in 10 of 26 patients (38.4%), and tumor mass completely disappeared in 4 patients (15.4%).

Nadir PRL levels and percent tumor shrinkage during CAB treatment in naive patients were significantly lower ($P < 0.001$) and higher ($P < 0.001$), respectively, than those in the remaining three groups, and the average weekly dose of CAB in resistant patients was significantly higher ($P < 0.001$) than that in the remaining three groups. A significant association was found between tumor shrinkage and previous treatments ($\chi^2 = 27.1$; $P < 0.0001$). At the multistep correlation analysis, nadir PRL levels were the strongest predictors of tumor shrinkage ($r^2 = 0.556$; $P < 0.0001$), followed by CAB dose ($r^2 = 0.577$; $P < 0.0001$). The tolerability was excellent in 105 patients (95.4%).

In conclusion, the prevalence of macroprolactinoma shrinkage after CAB treatment at standard doses for 1–3 yr was higher in naive patients (92.3%) than in intolerant (42.1%), resistant (30.3%), and responsive patients (38.4%). Thus, CAB can be employed as first line therapy in macroprolactinomas. The more PRL levels were suppressed, the more tumor shrinkage was obtained. (*J Clin Endocrinol Metab* **85:** 2247–2252, 2000)

CABERGOLINE (CAB) is a long-lasting dopamine agonist, characterized by a longer half-life of about 65 h and a higher affinity for D_2 dopamine-binding sites compared with bromocriptine (BRC) (1–3). In patients with tumoral hyperprolactinemia, treatment with CAB at a low weekly dose for 12–24 months was shown to induce a significant tumor volume reduction and serum PRL level normalization (1, 4, 5). In patients with microprolactinoma or nontumoral hyperprolactinemia (6–9), when pregnancy is not the main aim of treatment CAB is now considered the treatment of choice because of its efficacy and excellent patient compliance. CAB normalizes serum PRL levels and restores gonadal function in approximately 70% of patients

Received October 11, 1999. Revision received December 29, 1999. Rerevision received March 5, 2000. Accepted March 11, 2000.

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* This work was supported in part by Grant 9706151106 from MURST-Rome.

considered resistant or hyporesponsive to BRC or quinagolide (CV) (10, 11).

The efficacy of CAB treatment in patients with macroprolactinoma has been reported in only a small series of patients. It was demonstrated that a 12- to 24-month treatment with this compound at low weekly doses induced marked tumor shrinkage, with complete disappearance of the tumor in 26.1–36.4% of patients (12–14). Interestingly, these studies included patients who had never been treated with other dopamine agonists or who were briefly treated with BRC because of intolerance. In a multicenter study that included most patients (65 of 85) previously treated with other dopamine agonists before starting CAB treatment, tumor disappearance was documented in 8 of 62 (12.9%) patients (15). The prevalence of tumor shrinkage was significantly higher in the 20 naive patients than in the 65 previously treated with other dopamine agonists (82.3% *vs.* 60%) (15).

To investigate whether previous treatment with BRC or CV impaired a subsequent response to CAB in terms of tumor shrinkage, we prospectively evaluated the effect of 1–3 yr of treatment with this drug on 110 patients with macroprolactinoma.

Subjects and Methods

Patients

One hundred and ten patients with macroprolactinoma (70 women and 40 men, aged 17–79 yr) entered this study after their informed consent had been obtained. The patients were followed at the Department of Molecular and Clinical Endocrinology and Oncology, Federico II University of Naples, and Section of Endocrinology, Cardarelli Hospital of Naples. They were divided into 4 groups according to previous administration of dopamine agonists.

Naive group. Included were 26 patients (15 women and 11 men, aged 19–67 yr) who had never received medical treatment for hyperprolactinemia. Two of them had previously undergone unsuccessful surgery, but hyperprolactinemia and a well defined residual tumor at magnetic resonance imaging (MRI) persisted. Before starting CAB treatment, the serum PRL level was 1013.4 ± 277.7 μg/L (mean ± SEM), ranging from 185.5–5611 μg/L. Data for 13 patients were previously reported (13).

Intolerant group. Included were 19 patients (13 women and 6 men, aged 17–64 yr) who had previously undergone medical treatment with BRC for 7–60 days, which was discontinued because of the appearance of moderate to severe side-effects (nausea, vomiting, headache, postural hypotension, or dizziness) after initial administration of 2.5-mg doses of the drug. Before starting CAB treatment, a washout period of 15–40 days was undertaken by all but 3 patients who had visual field defects; the baseline serum PRL level was 539.4 ± 172.2 μg/L, ranging from 174-3564 μg/L. Data for 9 patients were previously reported (13).

Resistant group. Included were 37 patients (22 women and 15 men, aged 19–66 yr) shown to be resistant or hyporesponsive to BRC, CV, or both. In accordance with others, resistance to BRC was defined by the lack of PRL normalization after treatment with daily doses of at least 15 mg divided into at least 3 administrations for at least 3 months (16–19). Similarly, resistance to CV was defined by the lack of PRL normalization after treatment at a daily dose of at least 0.6 mg divided into at least 2 administrations for at least 3 months (11). During BRC or CV treatments, all 37 patients except 7 had a greater than 50% PRL decrease from baseline values, and 4 of 22 patients, with available tumor volume records at diagnosis, had a greater than 50% volume reduction. Eight of 37 patients had previously undergone unsuccessful surgery. Before starting CAB treatment, a washout period of 15–40 days was undertaken by all but 6 patients who had visual field defects, and the mean baseline serum PRL level was 602.6 ± 136.8 μg/L, ranging from 148-3511 μg/L. Data for 19 patients were previously reported (11).

Responsive group. Included were 28 patients (20 women and 8 men, aged 19–79 yr) who were treated previously with BRC or CV for 1–5 yr, achieving normoprolactinemia and restoration of gonadal function, but had discontinued BRC or CV because of compliance problems or because CV was no longer available. Some degree of tumor shrinkage had been obtained during a previous treatment(s), but a well defined tumor at MRI was present before starting CAB. In fact, among the 21 patients with available tumor volume record at diagnosis, various degrees of tumor shrinkage were observed in the majority of patients before starting CAB treatment (volume at diagnosis *vs.* pre-CAB treatment, 2262.8 ± 328.1 *vs.* 1335.6 ± 218.8 mm^3; $P < 0.001$). Fourteen of 28 patients were treated with CV for 12 months and were included in a 12-month open sequential study (20). Before starting CAB treatment, all patients withdrew from BRC or CV therapy for 15–30 days, and the mean baseline serum PRL level was 397 ± 43.1 μg/L, ranging from 140–978 μg/L.

Hypopituitarism was present in 2 naive and 2 resistant patients. Among naive, intolerant, and resistant patients, all men had decreased libido and impaired sexual potency, whereas all women had oligoamenorrhea; 18 patients had spontaneous or provoked galactorrhea, and 23 patients had visual field defects. Four women were of postmenopausal age (Table 1). The loss of libido was considered only in men due to the difficulty in assessing this symptom in women.

Study protocol

Four of 110 patients had hypopituitarism and received standard replacement therapy. At study entry, the serum PRL level was calculated as the average value for a 6-h course with hourly sampling (0800–1400 h). After 1, 2, 3, 6, 12, 18, 24, 30, and 36 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 was performed every month for the first 3 months and then quarterly. CAB (Pharmacia & Upjohn, Milan, Italy) treatment was started at a 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

TABLE 1. Clinical presentation and response to CAB treatment in 110 patients with macroprolactinoma

Symptoms	Naive patients 26 (15[a]/11)[b]		Intolerant patients 19 (13[a]/6)		Resistant patients 37 (22[a]/15)		Responsive patients 28 (20[a]/8)	
	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment
Oligoamenorrhea	14 (100)	1 (7.1)	12 (100)	0 (0)	21 (100)	1 (4.7)	0 (0)	0 (0)
Galactorrhea	4 (26.6)	0 (0)	6 (46.1)	0 (0)	8 (36.4)	0 (0)	0 (0)	0 (0)
Loss of libido	10 (90.9)	1 (9.1)	5 (83.3)	2 (33.3)	15 (100)	1 (6.7)	5 (62.5)	2 (25)
Loss of potency	11 (100)	2 (18.2)	6 (100)	3 (50)	15 (100)	1 (6.7)	5 (62.5)	2 (25)
Visual field defects	6 (23.7)	3 (11.1)	5 (26.3)	3 (15.8)	8 (21.6)	6 (16.2)	5 (62.5)	1 (3.6)
Headache	8 (30.7)	2 (7.7)	4 (21.1)	0 (0)	13 (35.1)	4 (10.8)	0 (0)	0 (0)

Data are shown as prevalence of symptoms at study entry and after treatment, expressed as number of affected patients and prevalence (%). W, Women, M, men.

[a] One woman in each group was menopausal.

[b] Number of patients (women/men).

was carried out on the basis of serum PRL suppression. Treatment was given at the maximal dose of 3.5 mg/week (0.5 mg/day) to 110 patients for 12 months, 104 patients for 24 months, and 81 patients for 36 months.

MRI studies

MRI studies were performed on clinical 0.5 T and 1 T scanners, using T1 weighted gradient recalled echo (repetition time, 200–300 ms; echo time, 10–12 ms; flip angle, 90°; 4 signal averages) and spin echo (repetition time, 400–500 ms; echo time, 20 ms; 2–3 signal averages) on 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 on the coronal plane). The acquisitions were repeated before and after the administration of 0.1 mmol gadolinium chelate (diethylenetriamine pentaacetate). MRI was performed before and after 12, 24, and 36 months of CAB treatment. Tumor shrinkage was evaluated as a greater than 80% reduction of the pretreatment tumor volume, calculated by the Di Chiro and Nelson formula: volume = height × length × width × $\pi/6$ (21). Tumor volume was calculated in all patients except 4 resistant and 2 responsive patients previously operated on and/or bearing small tumor remnants.

Visual perimetry

In all patients the assessment of visual field defects, by Goldmann-Friedmann perimetry, and visual acuity was performed at baseline. The ophthalmological examination was repeated every 3–6 months during the follow-up in patients with visual disturbances.

Assay

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 below 25 μg/L in women and 15 μg/L in men.

Statistical analysis

Data are reported as the mean ± SEM. The statistical analysis was performed with the SPSS (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%. Linear correlation analysis was carried out, calculating Pearson's coefficient, to assess the relationship among different parameters. Stepwise multiple linear regression was performed to evaluate the relative importance of PRL levels, either basal or nadir, basal tumor volume, and CAB dose on tumor shrinkage, evaluated as a percentage of baseline. The χ^2 test was also used where appropriate.

Results

Effects on PRL levels

Among the 26 naive patients, normoprolactinemia was achieved in 21 (80.7%) after 1–6 months at doses of 0.25–2 mg/week and in the remaining 5 patients after 24 months at doses of 0.5–3 mg/week. Among the 19 intolerant patients, normoprolactinemia was achieved in 18 (94.7%) after 1–6 months of CAB treatment (0.25–1 mg/week); in the remaining patient, mild hyperprolactinemia persisted (30.4 μg/L), as the CAB dose could not be increased up to 0.5 mg/week because of intolerance. Among the 37 resistant patients, normoprolactinemia was achieved in 19 (51.3%) after 6–12 months at doses of 1–2 mg/week and in the remaining 18 patients after 18–24 months when the dose was increased to 3–3.5 mg/week. However, stable normoprolactinemia was achieved in 26 patients (70.3%), whereas in the remaining 11, mild hyperprolactinemia recurred after normalization (31–55 μg/L). Among the 28 responsive patients, normoprolactinemia was achieved in 23 (82.1%) after 1–6 months at doses of 1–2 mg/week and in 5 patients after 12 months, increasing the dose to 3 mg/week. The nadir PRL level during CAB treatment in naive patients (2.3 ± 0.6 μg/L) was significantly lower than those in the remaining 3 groups of patients (7.7 ± 1.7, 7.9 ± 0.7, and 6.3 ± 0.9 μg/L; $P < 0.001$).

Effects on clinical symptoms

Table 1 shows the outcome of CAB treatment on clinical symptoms and signs in the different groups.

Effects on tumor mass

Evaluation of tumor shrinkage was performed in all but six resistant patients, who had very small tumor remnants at the beginning of treatment. Significant tumor reduction was observed in all patient groups after 1 yr (Fig. 1).

In the 26 naive patients tumor volume was reduced from 1431.5 ± 310.3 to 465.3 ± 116.7 mm^3 after 1 yr ($P < 0.001$) and was 47.2 ± 21.5 mm^3 after 3 yr of treatment ($P < 0.0001$). Tumor mass completely disappeared 16 patients (61.5%): in 5 after 1 yr, in 5 after 2 yr, and in 6 after 3 yr of CAB treatment. Significant tumor shrinkage (>80% of pretreatment volume) was obtained in another 8 patients (30.8%), in 1 patient tumor volume was reduced by 25–50%, and in the remaining patient tumor volume was reduced by 50–80% at the end of the CAB treatment period (Table 2).

In the 19 intolerant patients, tumor volume was reduced from 1925 ± 423.1 to 1242.5 ± 336.2 mm^3 after 1 yr ($P < 0.01$) and was 842.0 ± 330.7 mm^3 after 3 yr of treatment. Tumor mass completely disappeared in 4 of the patients (16%): in 2 after 2 yr and in 2 after 3 yr of CAB treatment. Significant tumor shrinkage (>80% of pretreatment volume) was obtained in another 4 patients (21.1%), and various degrees of tumor shrinkage were observed at the end of the CAB treatment period in the remaining 11 patients (Table 2).

In 22 of 33 resistant patients, tumor volume at diagnosis was slightly, but significantly, higher than that recorded before starting CAB treatment (1686.9 ± 252.3 *vs.* 1224.1 ± 236.3 mm^3; $P < 0.05$). However, in the 33 patients, tumor volume was reduced from 1208.0 ± 173.7 to 827.5 ± 130.0 mm^3 after 1 yr ($P < 0.005$) and was 471.2 ± 87.3 mm^3 after 3 yr of CAB treatment. Tumor mass did not disappear in any of the patients. Significant tumor shrinkage (>80% of pretreatment volume) was obtained in 10 patients (29.4%), but various degrees of tumor shrinkage were observed in the remaining 23 patients (Table 2).

In 21 of 26 responsive patients, tumor volume at diagnosis was significantly higher than that recorded before starting CAB treatment (2262.8 ± 328.1 *vs.* 1335.6 ± 218.8 mm^3; $P < 0.001$). In the 26 patients, tumor volume was further reduced from 1351.3 ± 181.5 to 958.7 ± 201.7 mm^3 after 1 yr ($P < 0.01$) and to 757.1 ± 193.6 mm^3 after 3 yr of CAB treatment. Tumor mass completely disappeared in 5 patients (19.2%): in 2 after 1 yr, in 2 after 2 yr, and in 1 after 3 yr of CAB treatment. Significant tumor shrinkage was obtained in another 5 patients (17.8%), but various degrees of tumor shrinkage were observed in the remaining 16 patients at the end of the CAB treatment period (Table 2).

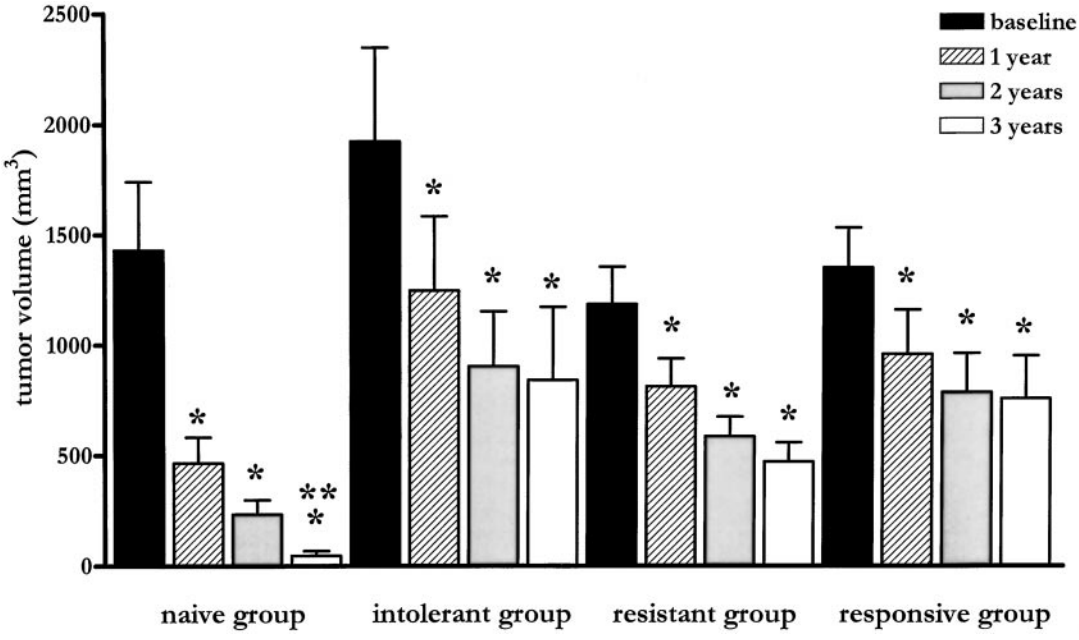

FIG. 1. Tumor volume (cubic millimeters) before and after 1, 2, and 3 yr of treatment in the four different groups of patients. *, $P < 0.01$ *vs.* pretreatment values; **, $P < 0.01$ *vs.* other three groups.

TABLE 2. Prevalence of prolactinoma shrinkage, measured in a semiquantitative way as absent (<25%), mild (26–50%), moderate (51–80%), and notable (>80%) of tumor volume reduction at magnetic resonance imaging compared to pretreatment values, and total volume shrinkage in different patient groups

	Absent shrinkage	Mild shrinkage	Moderate shrinkage	Notable shrinkage	Total shrinkage % (mean ± SEM)
26 naive patients	0	1	1	24	92.1 ± 2.9
19 intolerant patients	1	5	5	8	66.2 ± 6.4
33 resistant patients[a]	6	6	11	10	58.4 ± 4.9
26 responsive patients[a]	4	8	4	10	59.2 ± 6.2

[a] Number of patients with well defined tumor mass volume at study entry.

Tumor shrinkage obtained after 1 ($P < 0.001$) and 3 ($P < 0.001$) yr of CAB treatment in naive patients was significantly greater than that in the remaining three groups (Fig. 2). A significant association was found between the degree of tumor shrinkage and the response to previous treatment ($\chi^2 = 27.1$; $P < 0.0001$). In the entire group of patients, pretreatment tumor volume was significantly correlated with basal PRL levels ($r = 0.686$; $P < 0.001$), whereas the percentage of tumor shrinkage was inversely correlated with PRL nadir values ($r = -0.746$; $P < 0.001$). The CAB dose was inversely correlated with the percentage of tumor shrinkage ($r = -0.467$; $P < 0.001$) and was directly correlated with nadir PRL values ($r = 0.441$; $P < 0.001$). At the multistep correlation analysis, nadir PRL levels were the strongest predictors of tumor shrinkage ($r^2 = 0.556$; $P < 0.0001$) followed by CAB dose ($r^2 = 0.577$; $P < 0.0001$).

Tolerability

Tolerability of 3-yr treatment with CAB was excellent in all patients (95.4%), except five who reported mild nausea that spontaneously disappeared after a few weeks; one of them had postural hypotension that resolved without any additional treatment. No patient was withdrawn from CAB therapy because of side-effects. Among the five patients complaining of side-effects during treatment, two had been intolerant to BRC and CV treatment. The average weekly dose of CAB in resistant patients was significantly higher (2.4 ± 0.1 mg/week) than that in naive, intolerant, resistant, and responsive patients (1.7 ± 0.2, 1.8 ± 0.2, and 1.6 ± 0.1 mg/week; $P < 0.001$). All patients had excellent compliance during the 3 yr of CAB treatment.

Discussion

The most important finding of the present study is that patients with macroprolactinoma given CAB as the first line treatment achieved a lower PRL level and a higher percent tumor volume reduction than patients treated with other dopamine agonists before starting CAB treatment. In particular, the prevalence of tumor disappearance was significantly higher in the naive group than in the other three groups ($\chi^2 = 27.1$; $P < 0.0001$). This finding did not depend on a different dose level, as the average dose employed was similar in naive, intolerant, and responsive patients, whereas it was significantly higher in resistant patients. Beyond this expected latter result, in the entire group the CAB dose was inversely correlated with tumor volume shrinkage and was directly correlated with PRL nadir. These findings can be explained by the routine clinical practice of increasing the

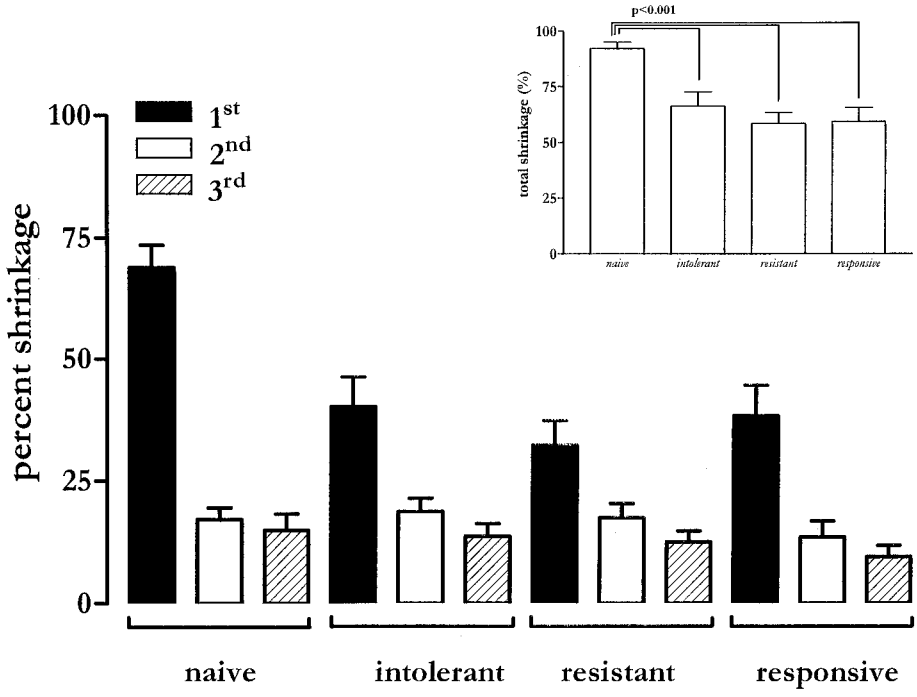

FIG. 2. Total percent shrinkage (superscript graph) and relative percent annual shrinkage after the first, second, and third years of treatment in naive, intolerant, resistant, and responsive patients.

dose to achieve more potent effects in terms of tumor shrinkage and PRL suppression. Another interesting observation of this study is that the nadir PRL level was the strongest predictor of tumor reduction in the multistep analysis.

In the past decade, several studies had described CAB as an optimal compound in treatment of hyperprolactinemic syndromes (1, 4–15). CAB normalizes serum PRL levels and restores gonadal function in the majority of patients with nontumoral hyperprolactinemia, microprolactinoma, or macroprolactinoma (1, 4, 5). In both micro- and macroprolactinomas, CAB treatment induces notable tumor shrinkage, and disappearance of tumor mass was observed in 26.1–36.4% in different series (10–15, 22). In a very recent multicenter study of 181 patients with macroprolactinoma (23), CAB treatment induced tumor shrinkage in 67%, with improvement of visual field defects in 70% of patients. In another multicenter study, CAB treatment induced tumor shrinkage in 60% of patients previously treated with other dopamine agonists and in 82.3% of untreated patients (15). In our study, including 110 macroprolactinoma-bearing patients, a greater than 80% tumor volume shrinkage was observed in 52 patients (47.3%), and in 24 of them tumor mass completely disappeared during CAB treatment. The prevalence of tumor shrinkage varied in different series. In fact, 11 of 15 macroprolactinoma patients had 31% average tumor shrinkage, as reported by Biller *et al.* (12); 33 of 62 patients had a greater than 25% reduction in the maximal diameter of the adenoma, as reported by Ferrari *et al.* (15); Cannavò *et al.* (14) reported a reduction of the average tumor volume in all of their 11 patients; whereas Ciccarelli *et al.* (22) reported a shrinkage of 10–100% in 6 of 9 patients. In a previous study (13), we reported that 14 of 23 patients with macroprolactinoma (60.9%) had a greater than 80% tumor volume reduction during CAB treatment, but 21 of these 23 patients (91.3%) had a greater than 25% reduction of the maximal tumor diameter. In the present study, notable tumor shrinkage was also obtained in patients previously treated with other dopamine agonists, namely resistant and responsive patients. In the resistant group, CAB treatment induced PRL normalization in all, even if only 26 of the 37 had stable PRL normalization, and reduced tumor volume to at least 50% of basal values in more than half of the patients. None of these patients normalized PRL levels and only a minority had tumor shrinkage of a similar degree during previous administration of BRC or CV. Moreover, an additional benefit of CAB treatment was observed in the responsive group; notable tumor shrinkage occurred in 10 patients, who had already had 6–78.8% tumor shrinkage during the previous administration of BRC or CV. However, the prevalence of significant tumor shrinkage was higher in naive patients (92.3%) than in those that had already been treated with BRC or CV and discontinued treatment because of intolerance (42.1%), resistance (30.3%), or poor compliance (38.4%). As the average therapeutic dose used to normalize PRL levels was similar in naive, intolerant, and responsive patients, this cannot explain the effect of CAB treatment in the naive group. It is necessary to emphasize that in intolerant patients the dose had to be maintained in the low range to limit the appearance of side-effects, and this could have limited the effect on tumor shrinkage. In the resistant group, although all of the patients achieved normalization of PRL levels, the effect on tumor mass was less impressive than in the other groups despite using significantly higher doses of CAB. In this group the low prevalence of tumor shrinkage can be explained by the molecular mechanisms underlying the resistance to dopamine agonists, such as low number and affinity of D_2 receptors (24). It should be considered that some degree of tumor shrinkage was observed during the third year of treatment in all groups of patients, indicating that further tumor reduction is achievable if treatment is

continued. Interestingly, in the entire group of patients, the nadir PRL levels were shown to be the strongest predictors of tumor shrinkage, followed by CAB dose. This indicated that effective PRL suppression was directly related to tumor shrinkage.

Finally, the appearance of side-effects was minimal in our series, occurring in 4.5% of patients. Side-effects were mild and did not prevent continuation of treatment. It should be noted that our practice is to start with very low doses (0.25 mg once for the first week), which could prevent the occurrence of initial side-effects.

In conclusion, notable macroprolactinoma shrinkage was observed in 92.3%, with disappearance of tumor mass in 61.5%, of naive patients treated with CAB at standard doses for 12–36 months. Tumor shrinkage and/or disappearance were also observed in intolerant, resistant, and responsive patients previously treated with BRC or CV, but to a lesser degree. Thus, CAB should be employed as first line therapy in macroprolactinomas. The more effectively PRL levels are suppressed, the more evident the tumor shrinkage obtained.

Acknowledgment

We are indebted to Prof. E. R. Laws (Department of Neurosurgery, Charlottesville, VA) for kindly revising the manuscript.

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