Prospective Study of High-Dose Cabergoline Treatment of Prolactinomas in 150 Patients

Masami Ono, Nobuhiro Miki, Takakazu Kawamata, Rena Makino, Kosaku Amano, Toshiro Seki, Osami Kubo, Tomokatsu Hori, and Kazue Takano

Department of Medicine II (M.O., N.M., R.M., T.S., K.T.), Institute of Clinical Endocrinology, and Department of Neurosurgery (T.K., K.A., O.K., T.H.), Tokyo Women's Medical University, Tokyo162-8666, Japan

Context: Cabergoline fails to normalize hyperprolactinemia in a considerable proportion of prolactinomas, especially macroadenomas.

Objective: We examined the effect of individualized high-dose cabergoline treatment on hyperprolactinemia in prolactinomas.

Patients: The study included 122 women and 28 men (93 microadenomas and 57 macroadenomas). Forty-seven had undergone transsphenoidal surgery. According to the preceding medical treatment, the participants were separated into untreated (group U; n = 60), intolerant (group I; n = 64), and resistant (group R; n = 26) groups.

Interventions: We promptly increased cabergoline dose on the basis of individual prolactin levels. Length of treatment was 1 yr.

Results: Cabergoline normalized hyperprolactinemia in all patients except one. The proportion of prolactin normalization in both groups U and I was 83% at 3 months and 95% at 6 months. By contrast, that in group R was 35% at 3 months and 58% at 6 months. Mean cabergoline dose in milligrams per week at the time of prolactin normalization was 2.0 ± 0.3 in group U, 0.9 ± 0.1 in group I, and 5.2 ± 0.6 in group R. Prolactin normalization rate at the 3 mg/wk dose was 84% overall but only 35% in group R. Serum progesterone or testosterone levels, diminished in 122 women or 16 men, respectively, were recovered in all except one resistant and four postmenopausal or panhypopituitary patients.

Conclusion: Individualized high-dose cabergoline treatment can normalize hyperprolactinemia and hypogonadism in nearly all prolactinomas irrespective of tumor size or preceding treatments. Hyperprolactinemia could be controlled in poor responders within 1 yr with doses higher than 3 mg/wk. **(*J Clin Endocrinol Metab* 93: 4721–4727, 2008)**

The first-line treatment of prolactin (PRL)-producing pituitary tumors, prolactinomas, is administration of dopamine receptor agonists (1, 2). The standard dopaminergic agonist has been bromocriptine, whereas cabergoline, an ultralong-acting dopamine D_2 receptor agonist, has been increasingly used in recent years. Cabergoline is superior to bromocriptine in terms of both efficacy and tolerability (3, 4). With a higher affinity and selectivity to pituitary D_2 receptors and a longer half-life (43 h) in serum than bromocriptine, cabergoline exhibits a greater ability to normalize hyperprolactinemia and restores an ovulatory cycle in patients with tumoral and nontumoral hyperprolactinemia (4, 5). These clinical benefits can be shared by those patients who have been intolerant or resistant to bromocriptine or other dopamine agonists (6–8).

Many clinical investigators have provided information about how to treat hyperprolactinemia with cabergoline, including

Abbreviation: PRL, Prolactin.

0021-972X/08/$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2007-2758 Received December 17, 2007. Accepted September 11, 2008.

First Published Online September 23, 2008

For editorial see page 4643

starting doses, frequency of administration, dose escalation, effective doses, and adverse effects (3). In general, cabergoline is started at 0.25–0.5 mg/wk and given once or twice a week; the dose is escalated at 2- to 3-month intervals, and the therapeutic dose is distributed from 0.5–1.0 to 3.0–3.5 mg/wk in most cases (4–17). With this regimen, cabergoline achieved normalization of hyperprolactinemia in 81–96% of microprolactinomas and in 61–83% of macroprolactinomas (4–19). This demonstrates a fairly high success rate of cabergoline treatment but simultaneously reveals that despite cabergoline treatment, hyperprolactinemia persists in a considerable proportion of prolactinomas, especially macroadenomas.

In this prospective study, we carried out individualized high-dose cabergoline treatment for 1 yr to normalize hyperprolactinemia in 150 patients with prolactinomas. High-dose treatment means the use of higher than usual therapeutic doses and the prompt escalation of cabergoline doses. Among individual patients who showed varying degrees of drug responsiveness, this therapy was directed at poor responders: previously resistant patients whose PRL had not been normalized despite long-term treatment with high-dose bromocriptine and newly resistant patients who did not respond well to cabergoline despite receiving medical treatment for the first time. With this therapeutic strategy, we achieved a very high rate of PRL normalization without any dropout.

Patients and Methods

Patients

This clinical study included 150 patients with prolactinomas consisting of 122 women and 28 men (Table 1). Mean age was 33.4 yr (range 19–79 yr). This study was approved by the Medical Ethical Committee of Tokyo Women's Medical University. Informed consent was obtained from all patients. Of the 150 patients, 47 had undergone transsphenoidal surgery, and two of the surgical patients subsequently received radiotherapy before cabergoline treatment. Of the 122 women, 66 reported amenorrhea and 53 reported irregular menstrual cycles. Of the remaining three females, two were postmenopausal and one had postoperative panhypopituitarism. Galactorrhea was observed in 39 female patients. Of the 28 male patients, 11 reported decreased libido and one of them had postsurgical panhypopituitarism. Visual field disturbances were reported by seven men only.

TABLE 1. Clinical characteristics of 150 patients with prolactinomas treated with cabergoline

	All (n = 150)	Group U (n = 60)	Group I (n = 64)	Group R (n = 26)
Sex	122 F/28 M	43 F/17 M	60 F/4 M	19 F/7 M
Age (yr)[a]	33.4 ± 9.7	32.3 ± 9.1	33.4 ± 8.6	36.3 ± 12.9
Basal PRL (μg/liter)[b]	570 ± 141	1065 ± 331	129 ± 15	515 ± 209
(Range)	(53–14,416)	(78–14,416)	(53–770)	(80–5,024)
Microadenoma	93	33	52	8
Macroadenoma	57	27	12	18
Surgery	47	10	19	18
Radiotherapy	2	0	0	2

Group U represents previously untreated patients, group I indicates patients intolerant to previous other dopamine agonist therapy, and group R shows those resistant to previous other dopamine agonist therapy. F, Female; M, male.

[a] Values are expressed as mean ± SD.

[b] Values are expressed as the mean ± SEM.

According to the preceding medical treatment, patients were divided into three groups (Table 1). Group U consisted of 60 previously untreated patients. Group I consisted of 64 patients who had shown intolerance to other dopamine agonists. Group R consisted of 26 patients who had shown resistance to other dopamine agonists. Patients in group I had a history of taking bromocriptine or terguride for 7 wk to 12 months but because of side effects could not continue to take a minimal effective dose of either drug every day. Patients in group R were those in whom bromocriptine failed to normalize hyperprolactinemia despite long-term (more than 6 months) treatment with high doses ranging from 15 to 75 mg/d. Of the 79 female patients in groups I and R, 58 wanted to conceive.

Diagnosis of prolactinomas

Prolactinoma was diagnosed by excluding disorders other than prolactinomas that cause hyperprolactinemia, demonstrating persistent hyperprolactinemia on at least three separate occasions, and detecting pituitary adenomas radiologically. Magnetic resonance imaging was used to visualize pituitary tumors and consisted of T1-weighted coronal and sagittal images before and after gadolinium injection and sagittal T2-weighted images.

Of the 150 prolactinomas, 93 were microadenomas less than 1 cm in diameter with serum PRL levels greater than 50 μg/liter and 57 were macroadenomas greater than 1 cm with PRL levels greater than 200 μg/liter, including 10 huge adenomas measuring greater than 3 cm in diameter. The final diagnosis was made after having confirmed unequivocal tumor shrinkage in response to medical treatments in nonsurgical patients or with immunohistochemical staining of excised adenomas in surgical cases. When adenomas were invisible on magnetic resonance imaging, cases were diagnosed as idiopathic hyperprolactinemia and those patients were excluded from this study.

Protocol of cabergoline treatment

Cabergoline was started at a standard weekly dosage and schedule, *i.e.* 0.25–0.5 mg twice a week. The starting doses were 0.25 mg for patients in groups U and I and 0.5 mg for patients in group R. A maximum daily dose was set at 3 mg/d, and when higher doses were required, cabergoline was given three to four times a week. Bromocriptine that had been given to resistant patients was switched to cabergoline after a 2- to 4-wk washout period. Serum PRL was measured every 2 wk for the first month and once a month thereafter until the end of this study. Cabergoline was incrementally dose adjusted on the basis of individual post-treatment PRL values until amelioration of hyperprolactinemia. This adjustment was carried out on the day of or within a few days after blood withdrawal for PRL measurement. For the initial 3 months, cabergoline was increased by 0.5 mg/wk at 2- to 4-wk intervals at a maximum incremental rate of 3 mg/wk per 3 months. Cabergoline was maintained at the dose at which PRL was first normalized. If PRL was not normalized at 3, 6, or 9 months, cabergoline was further increased at a maximum of 3 mg/wk in the next 3 months.

Drug compliance and side effects were carefully monitored by interview or through facsimile or E-mail. When side effects developed on dose escalation, medication was increased in smaller increments or at longer intervals than 2–4 wk, usually after side effects dissipated. Alternatively, cabergoline was given once more at the same dose, *i.e.* three times a week.

Hormone measurement

Serum PRL was measured by RIA or ELISA in our university laboratory using World Health Organization 2nd international reference preparation-PRL (83/562) as a reference preparation. The RIA kit (Eiken Chemical Co. Ltd., Tokyo, Japan) was used until January 2002, when it was substituted with the ELISA kit (Tosoh, Tokyo, Japan). The correlation coefficient (r) between PRL values measured by RIA and ELISA was 0.985. The normal range of serum PRL was 1.8–15 μg/liter for men and women at the nonovulatory, *i.e.* follicular or luteal, phase with either kit. Serum testosterone and progesterone levels were determined by ELISA kits (Roche Diagnostics Inc., Tokyo, Japan). The normal range of

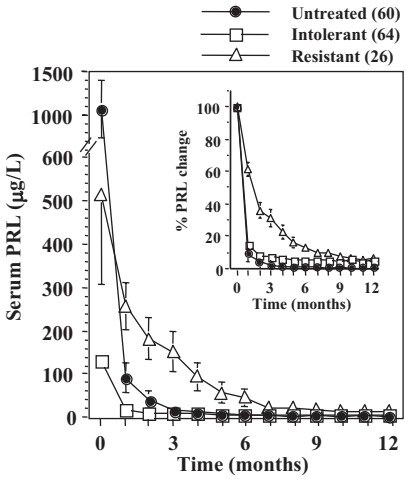

FIG. 1. Time course of changes in mean (±SEM) prolactin levels after cabergoline treatment in three groups of patients with prolactinomas. *Filled circle*, untreated; *open square*, intolerant; *open triangle*, resistant. The *number in parentheses* indicates the number of patients in each group. The *inserted figure* illustrates percent changes in mean prolactin levels with baseline values in each group being 100%. Error bars too small to plot were omitted.

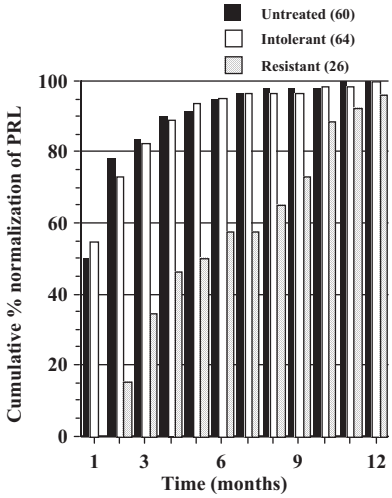

FIG. 2. Sequential changes in cumulative percent normalization rate of prolactin after cabergoline treatment in three groups of patients with prolactinomas. *Black column*, untreated; *white column*, intolerant; *hatched column*, resistant. The *number in parentheses* indicates the number of patients in each group.

testosterone in men was 284–799 ng/dl and that of progesterone in women was 0.2–1.5 ng/ml in the follicular phase and 1.7–27 ng/ml in the luteal phase.

Statistical analysis

Serum PRL, testosterone, and progesterone values and cabergoline doses are presented as means ± SEM. Statistical analysis was performed by paired *t* test or ANOVA followed by nonparametric Wilcoxon rank test where appropriate. A value of $P < 0.05$ was considered to be significant.

Results

Effects of cabergoline on serum PRL levels

Figure 1 shows time courses of changes in mean (± SEM) PRL levels after cabergoline treatment in three groups of patients. The *inserted figure* indicates percent changes in mean PRL values with pretreatment values in each group being 100%. Serum PRL levels before treatment are shown in Table 1. Cabergoline rapidly inhibited serum PRL levels in all three groups of patients. Elevated PRL in groups U and I showed a greater and more rapid decrease than that in group R in response to cabergoline; at 1 month, the decrease was 91.5% in group U and 85.2% in group I, in contrast to 53.4% in group R. Posttreatment PRL in groups U and I was stabilized at 3–4 months, whereas that in group R decreased progressively until 7 months and thereafter declined very slowly. Mean PRL fell into the normal range at 2 months in group I, at 4 months in group U, and at 10 months in group R.

Cumulative normalization rate of hyperprolactinemia

Figure 2 illustrates sequential changes in the cumulative percent normalization rate of hyperprolactinemia in three groups of patients. Normoprolactinemia was achieved by 1 month in 50.0% of the patients in group U and 54.7% in group I but in none in group R. By 3 months, PRL normalization increased to 83.3% in group U and 82.8% in group I but was only 34.6% in group R. Hyperprolactinemia persisted in 38 patients with a mean value of 64 ± 12.3 μg/liter (range 17–384 μg/liter). By 6 months, cumulative PRL normalization reached 95.0% in group U and 95.3% in group I, whereas that in group R remained lower, at 57.7%. At this time, 17 patients were hyperprolactinemic with a mean PRL level of 46 ± 8.2 μg/liter (range 18–157 μg/liter). The normalization rate of hyperprolactinemia in these 17 patients continued to rise slowly but steadily after 6 months, and by 12 months normoprolactinemia was achieved in all patients except one in group R (99.3%). This exceptional case was a woman with macroadenoma and multiple endocrine neoplasia type 1. The final PRL normalization rate in group R was 96.2%.

In terms of tumor size, cumulative PRL normalization rates at 3, 6, and 12 months were 86.0, 93.5, and 100%, respectively, in 93 microadenomas and 56.1, 80.7, and 98.2%, respectively, in 57 macroadenomas. Resistant adenomas accounted for 8.6% of microadenomas and 31.6% of macroadenomas (Table 1).

The number and cumulative percentage of patients who attained normoprolactinemia according to weekly cabergoline dosage

In Fig. 3A, the numbers of patients who attained normoprolactinemia are illustrated as three separate groups in terms of cabergoline dosage ranging from 0.5 to 12 mg/wk. In a majority of patients in groups U (81.7%) and I (98.4%), the weekly cabergoline dosage required for PRL normalization was distributed at low levels of 0.5–2.0 mg/wk, whereas no patient in group R attained PRL normalization with doses less than 2 mg/wk and 20 of the 26 patients (76.9%) required doses equal to or greater than 3 mg/wk. The mean weekly dose of cabergoline at the time of PRL normalization was 5.2 ± 0.6 mg in group R, which was significantly ($P < 0.0001$) greater than 2.0 ± 0.3 mg in group U or 0.9 ± 0.1 mg in group I.

Figure 3B shows the cumulative percentage of patients who achieved normoprolactinemia plotted against cabergoline doses ranging from 0.5 to 12 mg/wk. The absolute number of patients is shown beside each marking. In group I, normoprolactinemia

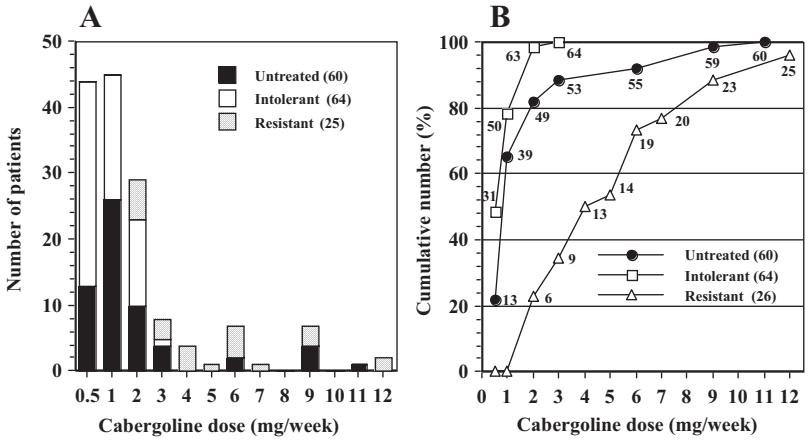

FIG. 3. Numbers of patients who achieved normoprolactinemia in terms of weekly cabergoline dosage. The *number in parentheses* indicates the number of patients in each of three groups. A, The absolute numbers of patients and cabergoline doses (milligrams per week). *Black column*, untreated; *white column*, intolerant; *hatched column*, resistant. B, The cumulative numbers (percent) of patients and cabergoline doses (milligrams per week). *Filled circle*, untreated; *open square*, intolerant; *open triangle*, resistant. The cumulative absolute numbers of patients are shown beside each marking.

was attained in 48.4% of patients at a dose as low as 0.5 mg/wk, in 78.1% at 1 mg/wk, and in all patients at 3 mg/wk. In group U, PRL was normalized in 21.7, 65.0, and 88.3% at doses of 0.5, 1, and 3 mg/wk, respectively, and dose escalation to 11 mg/wk was necessary to achieve complete normalization. On the other hand, hyperprolactinemia in group R was not normalized at a dose of 0.5–1.0 mg/wk. The rate of PRL normalization gradually increased to 34.6, 73.1, and 88.5% at 3, 6, and 9 mg/wk, respectively, finally reaching 96.2% at the highest dose of 12 mg/wk.

Overall PRL normalization rate in terms of weekly cabergoline dosage was 84.0% at 3 mg, 92.0% at 6 mg, and 97.3% at 9 mg.

Recovery of gonadal and visual function

Other than two postmenopausal women, one panhypopituitary woman, and one panhypopituitary man, 119 female and 27 male patients were evaluated for recovery from hyperprolactinemic hypogonadism after cabergoline treatment.

Of the 66 patients with amenorrhea, 65 resumed withdrawal bleeding. These 65 patients, along with 53 patients with irregular periods, had restored regular menstrual cycles. Mean serum progesterone in these 118 patients was 0.37 ± 0.01 ng/ml before treatment and rose to 12.6 ± 0.44 ng/ml ($P < 0.0001$), a value obtained at the presumed luteal phase, after PRL normalization (Table 2). Galactorrhea ceased in all 39 female patients after treatment. Diminished serum testosterone was observed in 15 men and was normalized in all of these patients, recovering from 64 ± 11 to 405 ± 32 ng/dl ($P < 0.0001$) after PRL normalization (Table 2). In the remaining 12 men, pretreatment testosterone was normal but apparently rose in 10 of these patients after PRL normalization, resulting in a significant increase in the mean value from 396 ± 37 to 537 ± 36 ng/dl ($P < 0.0001$). Decreased libido, reported by 10 of the 15 testosterone-deficient men, was recovered in all patients. Visual field defects disappeared in all seven men within 1–3 months after cabergoline treatment. Two of them belonged to group R.

Side effects of cabergoline

Of the 150 treated patients, 14 reported 19 events of side effects, which included headache (n = 6 patients), stomach discomfort (n = 4), dizziness (n = 3), constipation (n = 2), sleepiness (n = 1), anorexia (n = 1), nasal obstruction (n = 1), and leg edema (n = 1). All effects were minimal and transient, disappearing within 2–4 wk. There were no apparent psychiatric side effects. None of the patients dropped out during treatment.

Discussion

Cabergoline suppressed hyperprolactinemia in all patients with prolactinomas. There were no dropout or nonresponder patients. The 99.3% normalization rate of hyperprolactinemia that we achieved was greater than those previously obtained with

TABLE 2. Serum levels of progesterone in female patients and testosterone in male patients who had no irreversible change or damage on the pituitary-gonadal axis and achieved normoprolactinemia following cabergoline treatment

Hormones	Group	n	Before cabergoline	After cabergoline	*P* value
Progesterone (ng/ml) (Range)	Overall[a]	118	0.37 ± 0.01 (0.20–0.88)	12.6 ± 0.44[b] (3.3–25.4)	<0.0001
Testosterone (ng/dl) (Range)	Overall[c]	27	212 ± 37 (20–626)	464 ± 27 (288–793)	<0.0001
	Normal	12	396 ± 37 (288–626)	537 ± 36 (348–793)	<0.0001
	Deficient	15	64 ± 11 (20–195)	405 ± 32 (288–630)	<0.0001

Serum progesterone and testosterone presented as before and after cabergoline treatment are those determined before cabergoline administration and after normalization of hyperprolactinemia or resumption of regular menses, respectively. Hormone values in individual patients were obtained from single measurement or as means of two separate determinations before cabergoline and as means of at least three separate determinations after cabergoline. Data are presented as means ± SEM.

[a] Excluding one resistant, two postmenopausal, and one postoperative panhypopituitary women.

[b] Obtained at the presumed luteal phase.

[c] Excluding one postoperative panhypopituitary man.

bromocriptine (80–90%) (1, 2) or cabergoline (61–96%) (4–19) in patients with tumoral hyperprolactinemia or in a mixed population of patients with tumoral and nontumoral hyperprolactinemia. This result is of significance in that almost complete PRL normalization was accomplished in patients only with tumoral hyperprolactinemia, not including those with idiopathic hyperprolactinemia, which is known to be highly responsive to dopamine agonists (1, 2). In addition, we emphasize that achievement of normoprolactinemia was accompanied by spontaneous recovery from hypogonadism in all the patients who had no irreversible change or damage on the pituitary-gonadal axis. Therefore, appropriately individualized, high-dose treatment could be a strategy to render cabergoline fully efficacious against prolactinomas.

Because cabergoline is more potent than the former standard dopaminergic agonists, bromocriptine and terguride (4–8), whether cabergoline can improve normalization rate of hyperprolactinemia in a certain group of patients depends on drug intolerance and resistance rather than drug potency. To avoid some side effects such as dizziness and sleepiness, often manifested in young women treated with bromocriptine, cabergoline was prescribed after dinner or at bedtime. If significant side effects took place, we dealt with them by increasing the dose more slowly at intervals longer than 2–4 wk or increasing the number of medicine-taking days per week instead of increasing the dose per day. Once patients could tolerate a daily dose of 1 mg, side effects rarely occurred at higher doses. In addition, we advised patients to take cabergoline on an unscheduled day of the week when they became aware of having forgotten to take medication. These flexible countermeasures resulted in very high compliance and no dropout in the present study. After side effects are overcome with an appropriate mode of drug escalation, the success rate in normalizing hyperprolactinemia is largely determined by the treatment outcome of resistant adenomas.

There are three potential reasons we could achieve a very high rate of PRL normalization. The first is related to the dose of cabergoline used to treat resistant adenomas. The weekly dosage of cabergoline was reported to be 0.5–3.0 mg with the maximum dose being less than 3.5 mg/wk in most institutions of Western countries (4–7, 9–17). For instance, three independent investigators [Webster *et al.* (4, 10), Muratori *et al.* (12), and Colao *et al.* (7, 13, 15–17)] used 0.5–1.0, 0.5–3.0, and 0.5–3.5 mg/wk. Cabergoline at doses greater than 4 mg/wk has rarely been used to treat hyperprolactinemia. In a report of Verhelst *et al.* (19), only seven of 455 hyperprolactinemic cases (1.9%) were treated with such high doses of cabergoline. The mean weekly dose of cabergoline that we used to normalize hyperprolactinemia was 2.0 ± 0.3 mg in group U and 0.9 ± 0.1 mg in group I patients, which were similar to those reported by other researchers, whereas patients in group R required a higher dose of 5.2 ± 0.6 mg. At 3 mg/wk, a dose reported to be nearly maximum by others, we achieved 100% normalization in group I only, whereas the success rate declined to 88.3% in group U and to 34.6% in group R. The dose that could normalize hyperprolactinemia in most patients (92.0%) was 6 mg/wk in our present study. Therefore, prolactinomas not completely responsive to 3 mg/wk cabergoline are probably resistant adenomas, and it should be attempted to escalate the dose to 6 mg/wk to successfully treat such cases. The effective dose of cabergoline in group U was distributed widely from 0.25 to 11 mg/wk, and seven of 60 patients in this group required a dose equal to or greater than 6 mg/wk. This indicate approximately 12% of our untreated prolactinomas would be cabergoline resistant.

The second reason is related to the mode of dose escalation of cabergoline. We carried out the dose increase of cabergoline more promptly than many clinical investigators of other institutions (7–10, 13, 15–17, 19). Especially during an early phase of treatment, cabergoline dose was adjusted at 2- to 4-wk intervals and by 3 months after initiation of treatment, hyperprolactinemia was controlled in 74.7% of patients. Upon starting cabergoline therapy, we assumed that there must be a certain proportion of tumors that are resistant to cabergoline, as is well known for bromocriptine (1, 2). One underlying mechanism for drug resistance involves a low level of expression of dopamine receptors, which is inherent in the nature of some adenomas (20, 21). The other mechanism that we have postulated involves estrogen-inducible functional resistance, which develops after cabergoline treatment. Estrogen stimulates PRL synthesis and secretion by disrupting the inhibitory action of dopamine (22–25). Some evidence suggests that decreased estrogen in hyperprolactinemic amenorrhea is restored beginning before rather than after complete amelioration of hyperprolactinemia because substantial reductions in PRL levels to still slightly elevated levels often was enough to restore ovulation and menses in such patients receiving bromocriptine therapy (2). In our present study, 22 of the 66 amenorrheic women resumed menstruation 1–6.6 months earlier than PRL normalization after cabergoline treatment (data not shown). It seems worthwhile therefore to reduce the antagonistic action of estrogen against dopamine agonists. The concomitant use of aromatase inhibitor with cabergoline is useful for some male patients with low testosterone (26), but it is unsuitable for female patients who want to recover gonadal function. We addressed this issue by rapidly reducing hyperprolactinemia and thereby shortening or minimizing the period of exposure to rising estrogen before achieving PRL normalization. Such rapid suppression of hyperprolactinemia would have contributed considerably to achieving normoprolactinemia at a very high rate.

The third reason appears to relate to the length of cabergoline therapy. Our present results showed that the cumulative normalization rate of hyperprolactinemia reached greater than 80% in groups U and I within 3 months after initiation of cabergoline, whereas that in group R was only 34.6% at 3 months, 57.7% at 6 months, and finally reached the maximum level of 96.2% by 1 yr. Therefore, at least 6 and possibly 12 months of treatment with a sufficient dose would be required in evaluating treatment outcome of such cabergoline-resistant adenomas. This view is supported by another treatment course of seven potentially cabergoline-resistant patients who were mixed in group U. With doses equal to or higher than 6 mg/wk, hyperprolactinemia was normalized in two patients at 6 months and one patient at each of 7, 8, and 11 months (Figs. 2 and 3). It is difficult to compare outcomes between short-term and long-term cabergoline treatments performed by other institutions because they evaluated

treatment outcomes by combining those obtained from short-term (<6 months) and long-term (>6 months) treatments and did not describe the proportion of PRL-normalized patients with respect to the length of treatment (6, 7, 9, 14, 18, 19). Judging from the separate reports from a single institution of Colao *et al.* (13, 15, 16), who dealt with macroprolactinomas, PRL normalization appears to increase, depending on the length of cabergoline treatment. The percentage of PRL normalization was 64.0% after 6 months treatment of 107 patients (16), whereas it was 82.6% as a consequence of 12–24 months treatment of 23 patients (13). Furthermore, in another of their papers that involved 110 macroadenomas, hyperprolactinemia was normalized in 73.6% of patients by 6 months and 89.1% at 24 months of treatment (15). These reports, together with present results, indicate that prolactinomas resistant or poorly responsive to cabergoline should be treated for a sufficient length, at least 1 yr.

Recently cardiac valvulopathy has been reported in patients with Parkinson's disease who received long-term treatment with high-dose cabergoline, doses especially exceeding 3 mg/d (21 mg/wk) (27, 28). In comparison, our endocrine patients gained disease control with much lower doses of cabergoline (0.25–12 mg/wk). Moreover, echocardiographic screening revealed that none of the 106 patients who after completion of this study continued to take cabergoline at 1 mg/wk or greater doses had any clinically significant valvulopathy (data not shown). Very recently Lancellotti *et al.* (29) reported a similar negative result in 112 patients with hyperprolactinemia treated with 0.25–4.5 mg/wk doses of cabergoline for 1–19 yr. Taken together, exposure to cabergoline appears to be safe for endocrine patients with hyperprolactinemia. However, echocardiographic surveillance may be warranted, especially in resistant patients who require high-dose cabergoline for a long period. Cabergoline can shrink and often extinguish the tumor mass within a few years (15). This bulk reduction may allow reduction of the drug to the lowest effective dose and perhaps even its complete withdrawal.

Acknowledgments

Address all correspondence and requests for reprints to: Masami Ono, M.D., Department of Medicine II, Institute of Clinical Endocrinology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: miki-masa@abox3.so-net.ne.jp.

Disclosure Statement: The authors have nothing to disclose.

References

1. **Gillam MP, Molitch ME, Lombardi G, Colao A** 2006 Advances in the treatment of prolactinomas. Endocr Rev 27:485–534
2. **Molitch ME** 1999 Medical treatment of prolactinomas. Endocrinol Metab Clin North Am 28:143–169
3. **Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Laws E, Marek J, Scanlon M, Sobrinho LG, Wass JAH, Giustina A** 2006 Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf) 65:265–273
4. **Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF** 1994 A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. N Engl J Med 331:904–909
5. **Pascal-Vigneron V, Weryha G, Bosc M, Leclere J** 1995 Hyperprolactinemic amenorrhea: treatment with cabergoline vs bromocriptine. Results of a national multicenter randomized double-blind study. Presse Med 24:753–757
6. **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
7. **Colao A, Di Sarno A, Sarnacchiaro F, Ferone F, Di Renzo G, Merola B, Annunziato L, Lombardi G** 1997 Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. J Clin Endocrinol Metab 82:876–883
8. **Sarno AD, Landi ML, Cappabianca P, Di Salle F, Rossi FW, Pivonello R, Di Somma C, Faggiano A, Lombardi G, Colao A** 2001 Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. J Clin Endocrinol Metab 86: 5256–5261
9. **Ferrari C, Paracchi A, Mattei AM, de Vincentiis S, D'Alberton A, Crosignani P** 1992 Cabergoline in the long-term therapy of hyperprolactinemic disorders. Acta Endocrinol (Copenh) 126:489–494
10. **Webster J, Piscitelli G, Polli A, D'Alberton A, Falsetti L, Ferrari C, Fioretti P, Giordano G, L'Hermite M, Ciccarelli E, Crosignani PG, DeCecco L, Fadini R, Faglia G, Flamigni C, Tamburrano G, Ismail I, Scanlon MF** 1993 The efficacy and tolerability of long-term cabergoline therapy in hyperprolactinaemic disorders: an open, uncontrolled, multicentre study. Clin Endocrinol (Oxf) 39: 323–329
11. **Biller BMK, Molitch ME, Vance ML, Cannistraro KB, Davis KR, Simons JA, Schoenfelder JR, Klibanski A** 1996 Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline. J Clin Endocrinol Metab 81:2338–2343
12. **Muratori M, Arosio M, Gambino G, Romano C, Biella O, Faglia G** 1997 Use of cabergoline in the long-term treatment of hyperprolactinemic and acromegalic patients. J Endocrinol Invest 20:537–546
13. **Colao A, Di Sarno A, Landi ML, Cirillo S, Sarnacchiaro F, Facciolli G, Pivonello R, Cataldi M, Merola B, Annunziato L, Lombardi G** 1997 Long-term and low-dose treatment with cabergoline induces macroprolactinoma shrinkage. J Clin Endocrinol Metab 82:3574–3579
14. **Ciccarelli E, Grottoli S, Razzore P, Gaia D, Bertagna A, Cirillo S, Cammarota T, Camanni M, Camanni F** 1997 Long-term treatment with cabergoline, a new long-lasting ergoline derivate, in idiopathic or tumorous hyperprolactinemia and outcome of drug-induced pregnancy. J Endocrinol Invest 20:547–551
15. **Colao A, Di Sarno A, Landi ML, Scavuzzo F, Cappabianca P, Pivonello R, Volpe R, Di Salle F, Cirillo S, Annunziato L, Lombardi G** 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
16. **Colao A, Di Sarno A, Cappabianca P, Briganti F, Pivonello R, Di Somma C, Faggiano A, Biondi B, Lombardi G** 2003 Gender differences in the prevalence, clinical features and response to cabergoline in hyperprolactinemia. Eur J Endocrinol 148:325–331
17. **Colao A, Vitale G, Cappabianca P, Briganti F, Ciccarelli A, De Rosa M, Zarrilli S, Lombardi G** 2004 Outcome of cabergoline treatment in men with prolactinoma: effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. J Clin Endocrinol Metab 89:1704–1711
18. **Ferrari CI, Abs R, Bevan JS, Brabant G, Ciccarelli E, Motta T, Mucci M, Muratori M, Musatti L, Verbessem G, Scanlon MF** 1997 Treatment of macroprolactinoma with cabergoline: a study of 85 patients. Clin Endocrinol (Oxf) 46:409–413
19. **Verhelst J, Abs R, Maiter D, van den Bruel A, Vandeweghe M, Velkeniers B, Mockel J, Lamberigts G, Petrossians P, Coremans P, Mahler C, Stevenaert A, Verlooy J, Raftopoulos C, Beckers A** 1999 Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. J Clin Endocrinol Metab 84: 2518–2522
20. **Pellegrini I, Rasolonjanahary R, Gunz G, Bertrand P, Delivet S, Jedynak CP, Kordon C, Peillon F, Jaquet P, Enjalbert A** 1989 Resistance to bromocriptine in prolactinomas. J Clin Endocrinol Metab 69:500–509
21. **Brue T, Pellegrini I, Priou A, Morange I, Jaquet P** 1992 Prolactinomas and resistance to dopamine agonists. Horm Res 38:84–89
22. **Raymond V, Bealieu M, Labrie F, Boissier J** 1978 Potent antidopaminergic activity of estradiol at the pituitary level on prolactin release. Science 200: 1173–1175
23. **West B, Dannies PS** 1980 Effects of estradiol on prolactin production and

dihydroergocryptine-induced inhibition of prolactin production in primary cultures of rat pituitary cells. Endocrinology 106:1108–1113

24. **Maurer RA** 1982 Relationship between estradiol, ergocryptine, and thyroid hormone: effects on prolactin synthesis and prolactin messenger ribonucleic acid levels. Endocrinology 110:1515–1520
25. **Gooren LJ, van der Veen EA, van Kessel H, Harmsen-Louman W, Wiegel AR** 1984 Prolactin secretion in the human male is increased by endogenous oestrogens and decreased by exogenous/endogenous androgens. Int J Androl 7:53–60
26. **Gillam MP, Middler S, Freed DJ, Molitch ME** 2002 The novel use of very high doses of cabergoline and a combination of testosterone and an aromatase inhibitor in the treatment of a giant prolactinoma. J Clin Endocrinol Metab 87:4447–4451
27. **Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E** 2007 Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med 356: 29–38
28. **Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G** 2007 Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med 356:39–46
29. **Lancellotti P, Livadariu E, Markov M, Daly AF, Burlacu M-C, Betea D, Pierard L, Beckers A** 2008 Cabergoline and the risk of valvular lesions in endocrine disease. Eur J Endocrinol 159:1–5