Place of Cabergoline in Acromegaly: A Meta-Analysis

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Context: Cabergoline is widely considered to be poorly effective in acromegaly.

Objective: The aim of this study was to obtain a more accurate picture of the efficacy of cabergoline in acromegaly, both alone and in combination with somatostatin analogs.

Design: We systematically reviewed all trials of cabergoline therapy for acromegaly published up to 2009 in four databases (PubMed, Pascal, Embase, and Google Scholar). We identified 15 studies (11 prospective) with a total of 237 patients; none were randomized or placebo-controlled. A meta-analysis was conducted on individual data (n = 227).

Results: Cabergoline was used alone in nine studies. Fifty-one (34%) of the 149 patients achieved normal IGF-I levels. In multivariate analysis, the decline in IGF-I was related to the baseline IGF-I concentration ($\beta = 1.16$; $P < 0.001$), treatment duration ($\beta = 0.28$; $P < 0.001$), and baseline prolactin concentration ($\beta = -0.18$; $P = 0.01$), and with a trend toward a relation with the cabergoline dose ($\beta = 0.38$; $P = 0.07$). In five studies, cabergoline was added to ongoing somatostatin analog treatment that had failed to normalize IGF-I. Forty patients (52%) achieved normal IGF-I levels. The change in IGF-I was significantly related to the baseline IGF-I level ($\beta = 0.74$; $P < 0.001$) but not to the dose of cabergoline, the duration of treatment, or the baseline prolactin concentration.

Conclusion: This meta-analysis suggests that cabergoline single-agent therapy normalizes IGF-I levels in one third of patients with acromegaly. When a somatostatin analog fails to control acromegaly, cabergoline adjunction normalizes IGF-I in about 50% of cases. This effect may occur even in patients with normoprolactinemia. **(*J Clin Endocrinol Metab* 96: 1327–1335, 2011)**

Acromegaly, a disorder due to excess GH/IGF-I (1, 2), is still associated with early death (3, 4). Poor outcome is predicted by a mean GH level above 2.5 μg/liter in old GH immunoassays and by an IGF-I level above the age-adjusted normal value (3, 4). The current treatment aim is thus to reduce GH levels to less than 2.5 μg/liter in old assays (5) and to less than 1 μg/liter in new sensitive assays (6). Surgery remains the first-line treatment, but 20% of patients with microadenomas and 40 to 60% of patients with macroadenomas are not cured by surgery and require adjuvant medical therapy (1).

Dopamine agonists, most of which are ergot-derived, were initially used to halt lactation. Their use in the treatment of hyperprolactinemia was first proposed almost 40 yr ago (7). Physiologically, dopamine stimulates GH secretion (8), but Chiodini *et al.* (9) showed in 1974 that dopamine agonists paradoxically suppressed GH hypersecretion in patients with acromegaly; this was confirmed

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Abbreviation: ULN, Upper limit of normal.

TABLE 1. Charateristics of the studies evaluating the effects of cabergoline alone in patients with acromegaly

				Before cabergoline			
First author, year (Ref.)	Design of the study	No. of patients (M/F)	Mean age (yr)	IGF-I (ng/ml), mean (SD)	IGF-I (% of ULN), mean (SD)	GH (ng/ml), mean (SD)	No. of patients with hyperprolactinemia
Ferrari, 1988 (29)	Prospective	6 (1/5)	48.7	1210 (507)	242 (101)	103 (134)	4
Jackson, 1997 (31)	Prospective	10 (3/7)	NA	739 (200)	NA	10 (7)	NA
Colao, 1997 (26)	Prospective	11 (4/7)	43.6	336 (46)	160 (22)	20.3 (10.4)	4
Muratori, 1997 (33)	Prospective	3 (1/2)	54.7	524 (23)	125 (5)	3.2 (0.85)	2
Abs, 1998 (25)	Prospective	60 (26/34)	51.1	677 (215)	213 (82)	16.2 (19.3)	20
Cozzi, 1998 (28)	Prospective	18 (7/11)	57.6	820 (312)	255 (88)	12 (13.2)	2
Vilar, 2002 (35)	Prospective	9 (5/4)	45.1	714 (116)	198 (32)	22.5 (8.8)	5
Freda, 2004 (30)	Prospective	14 (7/7)	46.0	544 (132)	145 (35)	1.3 (0.9)	6
Moyes, 2008 (32)	Prospective	15 (8/7)	55.5	474 (170)	NA	3.7 (3)	2
Sherlock, 2009 (34)	Retrospective	14 (NA)	NA	418 (171)	171 (55)	5.8 (4.7)	7

NA, Not available.

by *in vitro* studies performed on GH-secreting adenomas (10). The presence of dopamine binding sites, not only on mixed PRL-GH-secreting adenomas but also on pure GH-secreting adenomas, was demonstrated in binding studies (11, 12), and D2 receptor expression was later confirmed by several groups (13, 14). Finally, Rocheville *et al.* (15) suggested that D2 receptors and type 5 somatostatin receptors could heterodimerize, thus enhancing the functional activity of both agonists.

Cabergoline, an ergot derivative dopamine agonist, has been used for three decades in the treatment of Parkinson's disease (16) and hyperprolactinemia (17, 18). Being more effective and better tolerated than bromocriptine, cabergoline was also tested as a treatment for acromegaly, but its potential value was overshadowed by the advent of somatostatin analogs such as octreotide and lanreotide, which were shown to normalize IGF-I in 42–68% of patients (19–22). By comparison, bromocriptine was considered to normalize GH/IGF-I levels in only around 10% of cases (23). Clinical trials of cabergoline in acromegaly were mostly small and gave variable results (24–35); a larger trial (25) suffered from a failure to use age-adjusted normal IGF-I values. Moreover, none of these trials was randomized or placebo-controlled. This led to the general opinion that cabergoline was poorly effective, or that it was only effective in patients with mild residual disease or mixed GH/prolactin-secreting tumors (36). Combination therapy with somatostatin analogs and cabergoline was also tested in patients whose IGF-I levels failed to normalize on somatostatin analog monotherapy, but the results were also highly variable (37–41).

The aim of this study, based on a meta-analysis of all published reports, was to obtain a more accurate picture of the efficacy of cabergoline in acromegaly, both alone and in combination with somatostatin analogs.

Materials and Methods

Identification of relevant trials

All studies of cabergoline in acromegaly (the two key words) were systematically reviewed up to the end of 2009. The search strategy was unrestricted. Thirteen prospective and four retrospective studies (24–35, 37–41) were identified in four databases (PubMed, Pascal, Embase and Google Scholar). None were randomized controlled trials. Two studies were excluded, one (24) because it involved patients with McCune-Albright syndrome, and the other (27) because the patients were adolescents and the data were incomplete or uninterpretable because of intercurrent neurosurgical treatment. Finally, some of the data from the study by Jackson *et al.* (31), and particularly IGF-I levels, could not be used because the authors did not provide us with individual data lacking in the published article.

Data extraction

Data were extracted from published reports by two meta-analysts (P.M. and L.S.). Discrepancies were resolved by discussion among the authors of this report. Data for each individual participant were sought in each article. In four studies (28, 30, 33, 37), data had to be extracted from the figures. At our request, the authors of three studies (25, 34, 38) kindly provided complete individual data that were unavailable in the published reports. Details on one further patient were included in the Gatta *et al.* study (38) after publication. Individual data were only available for 60 of the 64 patients in the original publication of Abs *et al.* (25).

The studies were generally of good quality, with few losses to follow-up and the use of appropriate statistical methods.

The following data were extracted: mean age, gender distribution, number of patients included, therapy for acromegaly before cabergoline (surgery, radiotherapy, somatostatin analog, or another dopamine agonist), the nature of the adenoma (pure GH-secreting or mixed prolactin/GH-secreting) and its size (micro- or macroadenoma if not previously operated on, remnant of more or less than 1 cm in diameter if previously operated on, empty sella), intercurrent treatments during the study (somatostatin analogs), the final cabergoline dose, the treatment duration, side effects, the effect on tumor size, the prolactin con-

		Under cabergoline						
Cabergoline mean dose (mg/wk)	Duration of treatment (months)	IGF-I (ng/ml), mean (SD)	% change in IGF-I	IGF-I (% of ULN), mean (SD)	% of patients with normal IGF-I	GH (ng/ml), mean (SD)	% of patients with GH < 2.5 ng/ml	Tumor shrinkage (no. of patients)
0.85	2.6	541 (224)	50	108 (45)	50	9.5 (8.7)	0	1
7	4	473 (139)	36	NA	NA	3.1 (1.5)	20	NA
1.5	6	246 (29)	26.5	117 (14)	0	9.5 (4)	0	0
3	24	295 (73)	43	70 (17)	100	1 (0.64)	100	0
3.31	13.5	400 (217)	41	136 (76)	38	5.81 (9.4)	57	13
2.75	6	466 (284)	42	147 (88)	28	5.7 (7.5)	22	3
2.89	3	510 (180)	29.5	141 (50)	33	5.9 (5.6)	33	Not assessed
1.43	6	490 (149)	9	130 (43)	21	1.2 (1.3)	79	0
2.4	6	326 (179)	28	NA	33	1.7 (1.3)	73	Not assessed
0.96	12	334 (142)	18	137 (47)	50	4.2 (3.4)	43	Not assessed

centration at baseline, the GH (random) and IGF-I concentrations at baseline and the end of follow-up [or the nadir in two studies in which end-of-follow-up values were not available (26, 40)], the decline in GH and IGF-I during treatment, and losses to follow-up.

IGF-I, GH, and prolactin levels, when originally expressed in milli-international units per liter, were converted to nanograms per milliliter for this study, the conversion factor depending on the assay method indicated in the publication. IGF-I was also expressed as a percentage of the upper limit of the age-adjusted normal range (%ULN) when the age-adjusted normal range of the corresponding assay was available (the case for 134 patients on cabergoline and all patients on combination therapy). For 15 additional patients receiving cabergoline (32), IGF-I was considered to have normalized if the IGF-I SD score was below 1.2.

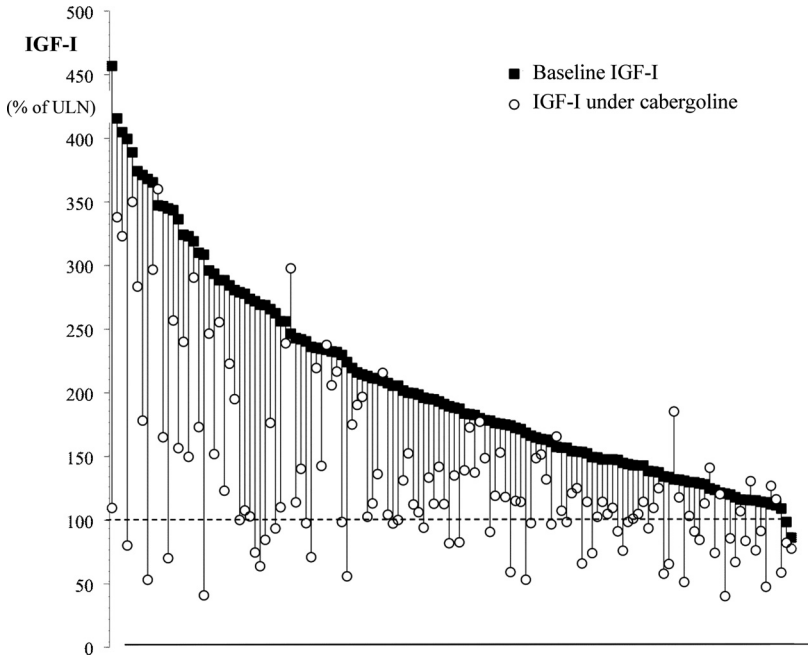

FIG. 1. Individual IGF-I levels, expressed as a percentage of the age-adjusted ULN range before (*black squares*) and after treatment with cabergoline (*open circles*) in patients with acromegaly.

Statistical analysis

The results are expressed as the mean (SD), median and range, or percentage. IGF-I levels are also expressed as a percentage of the age-adjusted ULN of the relevant assay.

All analyses were conducted on individual data. The following factors potentially predictive of IGF-I normalization were tested in univariate and multivariate (logistic regression) analyses: surgery, radiotherapy, macroadenoma (or remnant), microadenoma (or empty sella), sex, body mass index, age at diagnosis, cabergoline dose, treatment duration, associated medications, and baseline prolactin, IGF-I, and GH concentrations. In both models, interaction and study effects were taken into account. These parameters were analyzed for their influence on changes in IGF-I and GH by means of univariate and multivariate (linear regression) analysis. All significant parameters in univariate analysis were introduced in multivariate analysis. A significant interaction was found in all models between the dose of cabergoline or somatostatin analog and baseline hormone (IGF-I or GH) concentrations.

The χ^2 test (or Fisher's test) and Student's paired or unpaired *t* test were used to compare subgroups of patients (*e.g.* patients in Abs' study *vs.* the others; and patients with hyperprolactinemia *vs.* patients with normal prolactinemia). All analyses were conducted with SPSS 17.0 statistical software (SPSS Inc., Chicago, IL).

Results

Patients treated with cabergoline alone

Characteristics of the 10 trials of cabergoline single-agent therapy are shown in Table 1. All but one of these studies were open and prospective, and a total of 160 patients were enrolled. Individual data were available for only 150 patients.

TABLE 2. Characteristics of the published studies evaluating the effects of cabergoline in association with somatostatin analogs in patients with acromegaly

First author, year (Ref.)	Design of the study	No. of patients (M/F)	Mean age (yr)	Before cabergoline (under somatostatin analog alone)				
				Type of somatostatin analog treatment	IGF-I (ng/ml), mean (SD)	IGF-I (% of ULN), mean (SD)	GH (ng/ml), mean (SD)	No. of patients with hyperprolactinemia
Marzullo, 1999 (40)	Prospective	10 (7/3)	44.5	Lanreotide LP 30 mg/10 d	483 (264)	140 (64)	20.6 (29.5)	8
Cozzi, 2004 (37)	Prospective	19 (7/12)	54	Octreotide LAR 30 mg/28 d (n = 13) or lanreotide 60 mg/28 d (n = 6)	554 (188)	166 (63)	6.6 (3.7)	3
Selvarajah, 2005 (41)	Retrospective	4 (NA)	52.2	Octreotide LAR 30 mg/28 d	423 (175)	155 (23)	2.6 (0.3)	2
Gatta, 2005 (38)	Retrospective	10 (7/3)	40.6	Octreotide LAR 30 mg/28 d	524.4 (181)	216 (111)	4.1 (3.2)	0
Jallad, 2009 (39)	Prospective	34 (17/7)	47.7	Octreotide LAR 30 mg/28 d	571 (356)	197 (118)	5 (7.2)	13

M, Males; F, females; NA, not available.

The mean (SD) duration of treatment was 10.8 (8.2) months (range, 1–45; median, 7.5). Mean age was 50 (12) yr (range, 17 to 92). At baseline, mean IGF-I and GH levels were 634 (279) and 16 (34) ng/ml, respectively. Forty-six (38%) patients also had increased baseline prolactin levels. The mean prolactin level was 62 (216) ng/ml. Among the 82 patients who had been surgically treated and for whom immunostaining results for the excised adenoma were available, 30.5% had positive prolactin immunostaining. Among the 110 patients for whom the information was provided in the publication, the maximal diameter of the tumor before cabergoline initiation was more than and less than 1 cm in 53 and 57 cases, respectively.

Cabergoline was used as the first-line treatment for 29 patients (21% of the 136 patients for whom information on previous treatments was available). Of the remaining 107 patients, 75 and 35 patients, respectively, had previously been operated on and/or irradiated; 57 had received prior medical treatment, which had obviously been interrupted before the study. The cabergoline doses ranged widely from 0.3 to 7 mg/wk (one to seven administrations per week). The mean maximal dose was 2.6 (1.5) mg/wk, generally administered twice weekly.

Taking into account individual data available for 150 patients, cabergoline treatment was associated with significant reductions in IGF-I and GH levels of 33 and 47%, respectively (both $P < 0.001$). Fifty-one of 149 (34%) patients achieved age-adjusted normal IGF-I levels (Fig. 1). GH levels were below 2.5 ng/ml in 72 (48%) of 149 of patients. Mean IGF-I concentrations fell significantly from 655 (281) to 409 (215) ng/ml, and from 208 (81) to 133 (67)% of the ULN ($P < 0.001$). In multivariate analysis ($R^2 = 0.57$), this change was significantly related to the baseline IGF-I concentration ($\beta = 1.16$; $P < 0.001$), treatment duration ($\beta = 0.28$; $P < 0.001$), and baseline serum prolactin concentration ($\beta = -0.18$; $P = 0.01$), and with a trend toward a relation with the cabergoline dose ($\beta = 0.38$; $P = 0.07$). Other parameters were not significant in univariate analysis. The mean GH level fell significantly from 16.1 (34.0) to 5.2 (16.3) ng/ml ($P < 0.001$). In multivariate analysis ($R^2 = 0.98$), this change was significantly related to the baseline GH level ($\beta = 1.14$; $P < 0.001$) and the cabergoline dose ($\beta = 0.07$; $P = 0.001$) and showed a trend toward a relation with the treatment duration ($\beta = 0.03$; $P = 0.09$). Other parameters were not significant in univariate analysis.

IGF-I normalization on cabergoline therapy was predicted in univariate analysis by the baseline IGF-I concentration [221% (80) of the ULN in the nonnormalized group *vs.* 184% (75) in the normalized group; $P = 0.01$] and previous radiotherapy (20% of patients in the nonirradiated group *vs.* 36% in the previously irradiated group; $P = 0.06$). Other parameters were not significant in univariate analysis. Multivariate analysis with adjustment for studies confirmed these results, with $R^2 = 0.993$ (0.987–0.999) for the baseline IGF-I level and $R^2 = 2.4$ (0.9–5.7) for radiotherapy. IGF-I normalization occurred in 53, 29, 25, and 26% of patients with baseline IGF-I values of less than 150, 150–199, 200–249, and more than 250% of ULN, respectively ($P = 0.04$).

Cabergoline adjunction to ongoing somatostatin analog therapy

In five studies, cabergoline was added to ongoing treatment with a somatostatin analog that had failed to normalize IGF-I (Table 2). Three prospective studies involved 63 patients, and two retrospective studies involved 14 patients (one patient was added after publication). The mean duration of combined treatment was 6.6 (4.1) months (range, 2–20; median, 6). Cabergoline was added to lanreotide or octreotide LAR in 16 and 61 patients, respectively.

Mean age was 48.2 (14) yr (range, 20–85; median, 49). Previous treatments consisted of surgery in 54 patients (70%) and/or radiotherapy in 22 patients (29%). By definition, all the patients had previously received a somatostatin analog, which was the only prior treatment in 20

Cabergoline mean dose (mg/wk)	Duration of treatment (months)	Under somatostatin analog and cabergoline					
		IGF-I (ng/ml), mean (SD)	IGF-I (% of ULN), mean (SD)	% change in IGF-I	% of patients with normal IGF-I	GH (ng/ml), mean (SD)	% of patients with GH < 2.5 ng/ml
3.5	3	340 (83)	100 (22)	25.7	50	6.1 (5.3)	40
2.6	7	457 (289)	130 (67)	28.7	42	4.6 (2.6)	21
1.1	14.2	423 (175)	155 (23)	27.3	50	1.58 0.4)	25
1.8	55.4	281 (133)	120 (91)	45.3	60	1.7 (1)	70
2.4	6.3	334 (170)	125 (64)	55.4	56	2.8 (4.1)	71

cases (26%). The cabergoline dose ranged between 1 and 7 mg/wk [mean, 2.5 (1.1) mg/wk]. At baseline, on somatostatin analog therapy alone, the mean IGF-I and GH levels were 542 (280) and 7.4 (12.5) ng/ml, respectively. Twenty-one patients (27%) had high serum prolactin levels at baseline. Among the 46 patients in whom immunostaining of the excised tumor was available, 21 (47%) had a mixed GH-prolactin adenoma.

Forty patients (52%) achieved normal IGF-I levels on combined treatment (Fig. 2). The mean decreases in the IGF-I and GH serum concentrations were 30 and 19%, respectively. The mean IGF-I concentration fell significantly from 542 (280) ng/ml [182 (98)% of ULN] on somatostatin analog therapy alone to 358 (201) ng/ml [122 (64)% of ULN] after cabergoline adjunction ($P < 0.001$). This change was significantly related to the baseline IGF-I level ($\beta = 0.74$; $P < 0.001$), but not to the dose of cabergoline, the duration of treatment, or the baseline prolactin concentration. In the 44 patients whose IGF-I level at diagnosis of acromegaly was available (before any treatment), cabergoline adjunction led to a further 22% reduction in the IGF-I level compared with single-agent somatostatin analog therapy.

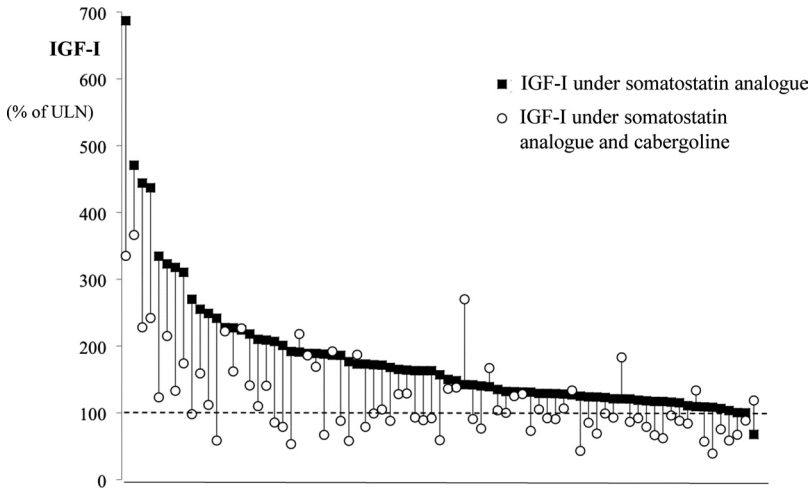

FIG. 2. Individual IGF-I levels, expressed as a percentage of the age-adjusted ULN range during treatment with somatostatin analogs alone (*black squares*) and after cabergoline adjunction (*open circles*) in patients with acromegaly.

IGF-I normalization at follow-up was predicted in univariate analysis by the baseline IGF-I concentration [222 (124)% of ULN in the nonnormalized group *vs.* 145 (40)% in the normalized group; $P < 0.001$] and the baseline GH concentration [11.3 (17) *vs.* 3.8 (3.5) ng/ml, respectively; $P < 0.01$]. Multivariate analysis with adjustment for studies confirmed the predictive value of the baseline IGF-I level only [$R^2 = 0.98$ (0.97–0.99)].

The mean GH concentration fell significantly from 7.4 (12.5) ng/ml on somatostatin analog therapy to 3.6 (3.8) ng/ml after cabergoline adjunction ($P < 0.001$). In multivariate analysis with adjustment for studies ($R^2 = 0.94$), the change in GH was related to the baseline GH concentration ($\beta = 0.99$; $P < 0.001$) but not to age, the dose, or the treatment duration.

Tumor shrinkage

The effect of cabergoline on tumor volume was examined prospectively in only five studies (25, 26, 29, 31, 33). Comparing patients in whom tumor volume decreased (n = 17) with other patients (n = 32), tumor shrinkage was associated with a higher baseline prolactin concentration [144 (350) *vs.* 33 (45) ng/ml; $P = 0.08$], a higher baseline IGF-I concentration [292 (97)% *vs.* 155 (39)% of ULN; $P < 0.001$] and previous treatment (47 *vs.* 19%; $P = 0.04$). The sample was too small for multivariate analysis.

Tolerability

Cabergoline was well tolerated. Side effects reported in 81 patients are detailed in Table 3. Due to lack of details in some studies and heterogeneity in reporting of the side effects, no analysis of the relationship between cabergoline dose or duration and side effects was possible. These side effects led to drug interruption in 12 of 227 patients (nine under cabergoline alone, and three under cabergoline and somatostatin analog); the dose at the time of cabergoline withdrawal was between 0.5 and 2 mg/wk. Cardiac

TABLE 3. Summary of the side effects as reported in the different studies using cabergoline alone or in combination with somatostatin analogs (SA) and incorporated in the meta-analysis

Side effects	Cabergoline alone	Cabergoline and SA	Total no.
Nausea	7	13	20
Headaches	4	7	11
Hypotension		7	7
Dizziness		6	6
Constipation	5	1	6
Mood disorders	5		5
Vesicular sludge		3	3
Raynaud's syndrome	1	1	2
Edema	2		2
Nasal congestion		2	2
Cramps	2		2
Others or nonspecified	14	1	15
Total	40	41	81

valve function was not evaluated in these studies. No comparison between studies with and without somatostatin analogs was attempted because side effects were not systematically reported.

Discussion

This systematic review refines the place of cabergoline, used either alone or in combination with somatostatin analogs, in the treatment of acromegaly. Based on IGF-I normalization, control of acromegaly is achieved in one third of patients when cabergoline is used alone and in more than half of patients when cabergoline is added to ongoing somatostatin analog therapy that has failed to normalize IGF-I.

Before the first specific drugs for acromegaly appeared, dopamine agonists were used to treat patients whose disease remained active after surgery and radiotherapy. However, bromocriptine was disappointing in this indication, normalizing IGF-I in only about 10% of patients (23). Somatostatin analogs subsequently superseded dopamine agonists. Although cabergoline seemed to be more effective, dopamine agonists were still considered poorly effective relative to somatostatin analogs (26, 36). Moreover, dopamine agonists were not licensed for use in acromegaly in many countries, including the United States.

Many studies have evaluated cabergoline in acromegaly (24–35, 37–41), but with variable results; depending on the study, cabergoline normalized IGF-I in 0 to 100% of patients! The largest study involved 64 patients who were divided into two groups according to their prolactin levels (25); a good response was defined by a decline in IGF-I to less than 300 ng/ml, regardless of the patient's age (no age-adjusted ULN was used). Cabergoline was found to be more effective in patients with hyperprolactinemia. Tumor shrinkage was observed in seven of the eight hyperprolactinemic patients with macroadenomas, and exceeded 50% in five cases. On reanalyzing individual data kindly provided by Dr. R. Abs, and using age-adjusted IGF-I ULNs, we found that IGF-I normalization was achieved in 42% of patients after cabergoline treatment (mean decline in IGF-I, 41%), whereas 57% of patients achieved GH levels below 2.5 ng/ml. It must be noted that the cabergoline doses were higher than in other studies (mean dose, 3.3 *vs.* 2 mg/wk; $P < 0.001$). Among 34 patients who were operated on and for whom tumor immunostaining results were available, eight had mixed PRL-GH-secreting adenomas, five of whom achieved normal IGF-I levels on cabergoline; this was the case for 11 of the 26 patients with pure GH-secreting adenomas. In the other studies, not only the efficacy results but also the dose of cabergoline, the duration of treatment, the levels of baseline GH and IGF-I, and the presence of hyperprolactinemia were very variable from one study to the other; performing a meta-analysis was the best way to clarify these points. Due to the low number of patients included in the majority of the studies, a pooled analysis may also help to find predictive factors of efficacy by using univariate and multivariate analysis.

This meta-analysis shows that the efficacy of cabergoline is dependent on the IGF-I baseline level; as with all other treatments for acromegaly (19, 42, 43), the chances of achieving a normal IGF-I level increase as the basal IGF-I level decreases. However, IGF-I levels normalize in some patients with very high baseline IGF-I levels (Fig. 1), suggesting that cabergoline might be worth trying in all acromegalic patients who require medical treatment.

The cabergoline dose ranged between 0.5 and 7 mg/wk in published studies. We observed only a trend toward a relationship between the cabergoline dose and the decline in IGF-I, whereas the relationship was significant for GH. Thus, sensitivity to cabergoline appears to be variable and more or less independent of the dose; some patients had good responses to low doses, whereas others were resistant to higher doses. In the group of responder patients who achieved normal IGF-I levels, the mean cabergoline dose was 2.5 (1.4) mg/wk, which is two to five times higher than the usual dose recommended for hyperprolactinemia (17), yet adverse effects did not appear to be more frequent than in patients treated for hyperprolactinemia (44–46). However, the doses used for acromegaly remain far below those used in Parkinson's disease, which have been linked to a risk of cardiac valve disease (47, 48). This adverse effect is unlikely in patients treated for hyperprolactinemia (reviewed in Ref. 49) and has never been reported in patients with acromegaly, although regular echocardio-

graphic surveillance may be warranted given the elevated baseline risk of myocardiopathy and valvulopathy in acromegaly (50, 51).

It is frequently claimed that the efficacy of cabergoline in acromegaly wanes with time. This is supported by the results of one study (30) in which eight of 14 patients achieved normal IGF-I levels after 6 months but only three patients still had normal levels at the end of follow-up. In two other studies (26, 40), efficacy was judged only on the basis of the IGF-I nadir rather than the values at the end of follow-up, suggesting that IGF-I levels might have increased after the nadir. However, our meta-analysis, including reanalysis of data of Abs *et al.* (25) (including intermediate IGF-I values), identified no tendency to treatment escape or tachyphylaxis. Moreover, the mean duration of treatment was 15 months in the responder group. Finally, the relationship between the duration of treatment and the decline in IGF-I levels found in our meta-analysis does not support any waning of the effect of cabergoline with time. Nevertheless, because some patients with low response to cabergoline may have prematurely stopped the treatment and because it was impossible to obtain global individual data allowing a real "intent-to-treat" analysis, we cannot rule out a waning effect with time of cabergoline.

Because cabergoline normalized IGF-I levels in only one third of patients, it is important to identify those subjects most likely to respond. Our meta-analysis does not support the common view that hyperprolactinemia is predictive of the cabergoline response because we found only a trend toward a relationship. Even patients with normal baseline prolactin levels may be good responders; this was the case for 50% of the good responders in our study. In fact this is not unexpected because dopamine receptors were previously demonstrated on the surface of pure GH-secreting adenomas (11–14); moreover, it has been shown that GH secretions from these adenomas were able to be suppressed *in vitro* by dopamine agonists (10, 52). Previous treatment, and particularly radiotherapy, may be predictive of a better response, but this could be related to the resulting lower baseline IGF-I levels [249 (91) *vs.* 194 (68)% of ULN in previously untreated patients; $P < 0.001$). The factor most predictive of cabergoline efficacy in terms of IGF-I normalization is thus the IGF-I level at the outset of treatment. Indeed, the chances of achieving a normal IGF-I level on cabergoline are clearly better (around 50%) when IGF-I is less than 150% of ULN than when it is over 150% (around 30%).

Few studies have examined the effects of adding cabergoline to ongoing somatostatin analog therapy (37–41). Published data indicate that 42 to 56% of patients with failing somatostatin analog therapy achieve normal IGF-I levels when cabergoline is added. Based on individual IGF-I levels in the 77 patients included in the relevant studies, our meta-analysis confirms that cabergoline adjunction normalizes IGF-I levels in more than 50% of cases. A further 22% reduction in IGF-I levels was obtained when cabergoline was added. As with cabergoline single-agent therapy, the best predictor of cabergoline efficacy was a lower IGF-I level before treatment, again emphasizing that the amplitude of the effect of cabergoline depends on the IGF-I level and that the chances of normalizing the IGF-I level increase when the IGF-I level before cabergoline is not too high.

Finally, this meta-analysis shows that tumor shrinkage is observed in about one third of patients treated with cabergoline, a value lower than that reported with somatostatin analogs (53, 54). Contrary to the secretory response for which the mixed (prolactin-GH) nature of the adenoma was not predictive, the tumor response improved as the prolactin level increased.

This meta-analysis has several limitations. The first is the small size of available studies and the lack of randomized controlled trials. To circumvent this limitation, we decided to pool prospective and retrospective studies, and we made every effort to obtain individual data for each patient, either by extracting them from the publications or by asking the authors to provide them. The second limitation is the heterogeneity of the hormone assay methods used in the different studies. We therefore chose to express the IGF-I level not only in absolute terms (nanograms per milliliter) but also as a percentage of the age-adjusted ULN. This was the best way to compare the different studies. The variable baseline IGF-I levels in the different studies must be underlined: up to 1840 μg/liter in the study of Ferrari *et al.* (29) and near normal in studies of Muratori *et al.* (30) and Freda *et al.* (33). This suggests that, in some studies, patients were preselected on the basis of their IGF-I level, which might have influenced the observed efficacy of cabergoline. We chose not to focus on GH levels, owing to the use of different generations of GH assays from one study to another. When giving results concerning the effects of cabergoline in terms of GH levels less than 2.5 ng/ml, our objective was to provide global data that could be compared with those of the numerous previously reported studies about the effects of acromegaly treatment, whether medical, surgical, or by irradiation…even if we are aware that this "historical" cutoff may not correctly apply to more sensitive GH assays used in the more recent studies! A last bias is the interaction that we found between the cabergoline dose and the pretreatment IGF-I level, which suggests that higher doses may sometimes have been prescribed to patients with highly elevated IGF-I levels.

In conclusion, this meta-analysis suggests that cabergoline single-agent therapy has modest efficacy in acromegaly, one third of patients achieving normal IGF-I levels. Nevertheless, given its simplicity of use and low cost, cabergoline might qualify as a first-line medical therapy, particularly when surgery has failed to control the GH/IGF-I excess and IGF-I is only moderately elevated; when the IGF-I is below 150% of ULN, the patient has a 50% chance of achieving a normal level on cabergoline. In addition, cabergoline adjunction may be warranted when somatostatin analog therapy fails to normalize GH/IGF-I levels because the IGF-I level subsequently normalizes in about 50% of cases. This effect of cabergoline is observed when patients have normoprolactinemia. Whether or not this treatment is safe long term, particularly on valvular heart function, remains to be determined.

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References

1. **Chanson P, Salenave S, Kamenicky P, Cazabat L, Young J** 2009 Pituitary tumours: acromegaly. Best Pract Res Clin Endocrinol Metab 23:555–574
2. **Melmed S** 2006 Medical progress: acromegaly. N Engl J Med 355: 2558–2573
3. **Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP** 2008 Mortality in acromegaly: a metaanalysis. J Clin Endocrinol Metab 93:61–67
4. **Holdaway IM, Bolland MJ, Gamble GD** 2008 A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. Eur J Endocrinol 159:89–95
5. **Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K, Melmed S** 2000 Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 85:526–529
6. **Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, Trainer P, Ghigo E, Ho K, Melmed S** 2010 A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab 95:3141–3148
7. **Besser GM, Parke L, Edwards CR, Forsyth IA, McNeilly AS** 1972 Galactorrhoea: successful treatment with reduction of plasma prolactin levels by brom-ergocryptine. Br Med J 3:669–672
8. **Giustina A, Veldhuis JD** 1998 Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev 19:717–797
9. **Chiodini PG, Liuzzi A, Botalla L, Cremascoli G, Silvestrini F** 1974 Inhibitory effect of dopaminergic stimulation on GH release in acromegaly. J Clin Endocrinol Metab 38:200–206
10. **Spada A, Sartorio A, Bassetti M, Pezzo G, Giannattasio G** 1982 In vitro effect of dopamine on growth hormone (GH) release from human GH-secreting pituitary adenomas. J Clin Endocrinol Metab 55:734–740
11. **Bression D, Brandi AM, Nousbaum A, Le Dafniet M, Racadot J, Peillon F** 1982 Evidence of dopamine receptors in human growth hormone (GH)-secreting adenomas with concomitant study of dopamine inhibition of GH secretion in a perifusion system. J Clin Endocrinol Metab 55:589–593
12. **Serri O, Marchisio AM, Collu R, Hardy J, Somma M** 1984 Dopaminergic binding sites in human pituitary adenomas other than prolactinomas. Horm Res 19:97–102
13. **Stefaneanu L, Kovacs K, Horvath E, Buchfelder M, Fahlbusch R, Lancranjan L** 2001 Dopamine D2 receptor gene expression in human adenohypophysial adenomas. Endocrine 14:329–336
14. **Missale C, Nash SR, Robinson SW, Jaber M, Caron MG** 1998 Dopamine receptors: from structure to function. Physiol Rev 78:189–225
15. **Rocheville M, Lange DC, Kumar U, Patel SC, Patel RC, Patel YC** 2000 Receptors for dopamine and somatostatin: formation of hetero-oligomers with enhanced functional activity. Science 288: 154–157
16. **Nutt JG, Wooten GF** 2005 Clinical practice. Diagnosis and initial management of Parkinson's disease. N Engl J Med 353:1021–1027
17. **Gillam MP, Molitch ME, Lombardi G, Colao A** 2006 Advances in the treatment of prolactinomas. Endocr Rev 27:485–534
18. **Schlechte JA** 2003 Clinical practice. Prolactinoma. N Engl J Med 349:2035–2041
19. **Freda PU, Katznelson L, van der Lely AJ, Reyes CM, Zhao S, Rabinowitz D** 2005 Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. J Clin Endocrinol Metab 90:4465–4473
20. **Gillis JC, Noble S, Goa KL** 1997 Octreotide long-acting release (LAR). A review of its pharmacological properties and therapeutic use in the management of acromegaly. Drugs 53:681–699
21. **McKeage K, Cheer S, Wagstaff AJ** 2003 Octreotide long-acting release (LAR): a review of its use in the management of acromegaly. Drugs 63:2473–2499
22. **Murray RD, Melmed S** 2008 A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. J Clin Endocrinol Metab 93:2957–2968
23. **Jaffe CA, Barkan AL** 1992 Treatment of acromegaly with dopamine agonists. Endocrinol Metab Clin North Am 21:713–735
24. **Akintoye SO, Chebli C, Booher S, Feuillan P, Kushner H, Leroith D, Cherman N, Bianco P, Wientroub S, Robey PG, Collins MT** 2002 Characterization of gsp-mediated growth hormone excess in the context of McCune-Albright syndrome. J Clin Endocrinol Metab 87:5104–5112
25. **Abs R, Verhelst J, Maiter D, Van Acker K, Nobels F, Coolens JL, Mahler C, Beckers A** 1998 Cabergoline in the treatment of acromegaly: a study in 64 patients. J Clin Endocrinol Metab 83:374–378
26. **Colao A, Ferone D, Marzullo P, Di Sarno A, Cerbone G, Sarnacchiaro F, Cirillo S, Merola B, Lombardi G** 1997 Effect of different dopaminergic agents in the treatment of acromegaly. J Clin Endocrinol Metab 82:518–523
27. **Colao A, Pivonello R, Di Somma C, Tauchmanovà L, Savastano S, Lombardi G** 2007 Growth hormone excess with onset in adolescence: clinical appearance and long-term treatment outcome. Clin Endocrinol (Oxf) 66:714–722
28. **Cozzi R, Attanasio R, Barausse M, Dallabonzana D, Orlandi P, Da Re N, Branca V, Oppizzi G, Gelli D** 1998 Cabergoline in acromegaly: a renewed role for dopamine agonist treatment? Eur J Endocrinol 139:516–521

29. **Ferrari C, Paracchi A, Romano C, Gerevini G, Boghen M, Barreca A, Fortini P, Dubini A** 1988 Long-lasting lowering of serum growth hormone and prolactin levels by single and repetitive cabergoline administration in dopamine-responsive acromegalic patients. Clin Endocrinol (Oxf) 29:467–476
30. **Freda PU, Reyes CM, Nuruzzaman AT, Sundeen RE, Khandji AG, Post KD** 2004 Cabergoline therapy of growth hormone, growth hormone/prolactin secreting pituitary tumors. Pituitary 7:21–30
31. **Jackson SN, Fowler J, Howlett TA** 1997 Cabergoline treatment of acromegaly: a preliminary dose finding study. Clin Endocrinol (Oxf) 46:745–749
32. **Moyes VJ, Metcalfe KA, Drake WM** 2008 Clinical use of cabergoline as primary and adjunctive treatment for acromegaly. Eur J Endocrinol 159:541–545
33. **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
34. **Sherlock M, Fernandez-Rodriguez E, Alonso AA, Reulen RC, Ayuk J, Clayton RN, Holder G, Sheppard MC, Bates A, Stewart PM** 2009 Medical therapy in patients with acromegaly: predictors of response and comparison of efficacy of dopamine agonists and somatostatin analogues. J Clin Endocrinol Metab 94:1255–1263
35. **Vilar L, Naves L, Freitas MC, Oliveira Jr S, Lyra R** 2002 Eficácia da Cabergolina na Tratamento da Acromegalia. Arq Bras Endocrinol Metab 46:269–274
36. **Burt MG, Ho KK** 2003 Comparison of efficacy and tolerability of somatostatin analogs and other therapies for acromegaly. Endocrine 20:299–305
37. **Cozzi R, Attanasio R, Lodrini S, Lasio G** 2004 Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status. Clin Endocrinol (Oxf) 61:209–215
38. **Gatta B, Hau DH, Catargi B, Roger P, Tabarin A** 2005 Re-evaluation of the efficacy of the association of cabergoline to somatostatin analogues in acromegalic patients. Clin Endocrinol (Oxf) 63:477–478
39. **Jallad RS, Bronstein MD** 2009 Optimizing medical therapy of acromegaly: beneficial effects of cabergoline in patients uncontrolled with long-acting release octreotide. Neuroendocrinology 90:82–92
40. **Marzullo P, Ferone D, Di Somma C, Pivonello R, Filippella M, Lombardi G, Colao A** 1999 Efficacy of combined treatment with lanreotide and cabergoline in selected therapy-resistant acromegalic patients. Pituitary 1:115–120
41. **Selvarajah D, Webster J, Ross R, Newell-Price J** 2005 Effectiveness of adding dopamine agonist therapy to long-acting somatostatin analogues in the management of acromegaly. Eur J Endocrinol 152: 569–574
42. **Nomikos P, Buchfelder M, Fahlbusch R** 2005 The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. Eur J Endocrinol 152:379–387
43. **Barrande G, Pittino-Lungo M, Coste J, Ponvert D, Bertagna X, Luton JP, Bertherat J** 2000 Hormonal and metabolic effects of radiotherapy in acromegaly: long-term results in 128 patients followed in a single center. J Clin Endocrinol Metab 85:3779–3785
44. **Rains CP, Bryson HM, Fitton A** 1995 Cabergoline. A review of its pharmacological properties and therapeutic potential in the treatment of hyperprolactinaemia and inhibition of lactation. Drugs 49: 255–279
45. **Di Sarno A, 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
46. **Ono M, Miki N, Kawamata T, Makino R, Amano K, Seki T, Kubo O, Hori T, Takano K** 2008 Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. J Clin Endocrinol Metab 93:4721–4727
47. **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
48. **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
49. **Valassi E, Klibanski A, Biller BM** 2010 Clinical review: potential cardiac valve effects of dopamine agonists in hyperprolactinemia. J Clin Endocrinol Metab 95:1025–1033
50. **Pereira AM, van Thiel SW, Lindner JR, Roelfsema F, van der Wall EE, Morreau H, Smit JW, Romijn JA, Bax JJ** 2004 Increased prevalence of regurgitant valvular heart disease in acromegaly. J Clin Endocrinol Metab 89:71–75
51. **Colao A, Spinelli L, Marzullo P, Pivonello R, Petretta M, Di Somma C, Vitale G, Bonaduce D, Lombardi G** 2003 High prevalence of cardiac valve disease in acromegaly: an observational, analytical, case-control study. J Clin Endocrinol Metab 88:3196–3201
52. **Saveanu A, Lavaque E, Gunz G, Barlier A, Kim S, Taylor JE, Culler MD, Enjalbert A, Jaquet P** 2002 Demonstration of enhanced potency of a chimeric somatostatin-dopamine molecule, BIM-23A387, in suppressing growth hormone and prolactin secretion from human pituitary somatotroph adenoma cells. J Clin Endocrinol Metab 87:5545–5552
53. **Bevan JS** 2005 Clinical review: the antitumoral effects of somatostatin analog therapy in acromegaly. J Clin Endocrinol Metab 90: 1856–1863
54. **Melmed S, Sternberg R, Cook D, Klibanski A, Chanson P, Bonert V, Vance ML, Rhew D, Kleinberg D, Barkan A** 2005 A critical analysis of pituitary tumor shrinkage during primary medical therapy in acromegaly. J Clin Endocrinol Metab 90:4405–4410