Pituitary (2011) 14:148–156
DOI 10.1007/s11102-010-0272-1

Role of the addition of cabergoline to the management of acromegalic patients resistant to longterm treatment with octreotide LAR

Lucio Vilar · Monalisa F. Azevedo · Luciana Ansaneli Naves · Luiz Augusto Casulari · José Luciano Albuquerque · Renan M. Montenegro · Renan M. Montenegro Jr. · Patricia Figueiredo · Gilvan C. Nascimento · Manuel S. Faria

Published online: 21 November 2010

Abstract The aim of this prospective open trial was to evaluate the efficacy in normalizing IGF-I levels of the addition of cabergoline to the treatment of acromegalic patients partially responsive to Octreotide-LAR (OCT-LAR), a long acting somatotastin analog (SSA). Fifty-two patients who did not achieve hormonal control after long-term therapy (at least, 12 months) with OCT-LAR (30 mg every 28 days intramuscularly) were given cabergoline in addition to the SSA treatment. Normalization of IGF-I levels was achieved in 40.4% of patients by 6 months after the addition of cabergoline (1.0–3.0 mg/week; mean, 2.19 ± 0.64), and these patients were considered responsive. Compared to non-responsive subjects, responsive patients had significantly lower mean %ULNR-IGF-I and GH levels. However, the rate of hyperprolactinemia and positive immunohistochemical staining for PRL was similar in both groups, before the addition of cabergoline. Responsive patients were followed for at least 12 months on combination treatment and persisted with normal IGF-I levels. Patients with baseline %ULNR IGF-I up to 220% and/or GH up to 5 ng/ml were those who benefited the most from combination treatment. No patients with %ULNR-IGF-I > 250% reached normalization of IGF-I levels. Our findings demonstrated that the addition of cabergoline, even at relatively low doses, is effective in both short- and long-term control of IGF-I levels in acromegalic patients partially responsive to octreotide LAR, particularly in those with mild/moderately elevated GH/IGF-levels, irrespective of prolactin status.

Keywords Acromegaly · Cabergoline · Octreotide LAR · Combination therapy

L. Vilar · J. L. Albuquerque
Division of Endocrinology, Hospital das Clinicas, Federal University of Pernambuco, Recife, Brazil

M. F. Azevedo · L. A. Naves · L. A. Casulari
Division of Endocrinology, Brasilia University Hospital, Brasília, Brazil

R. M. Montenegro · R. M. Montenegro Jr. · P. Figueiredo
Division of Endocrinology, Hospital Walter Cantidio, Federal University of Ceará, Fortaleza, Brazil

G. C. Nascimento · M. S. Faria
Division of Endocrinology, Hospital das Clinicas, Federal University of Maranhão, São Luiz, Brazil

L. Vilar (✉)
Rua Clovis Silveira Barros, 84/1202, Boa Vista, Recife CEP 50.050-270, Brazil
e-mail: lvilar@gmail.com

Introduction

Transsphenoidal surgery has long been considered the treatment of choice for acromegaly [1–3]. However, even in experienced hands, the surgical intervention is successful in only about 50% of cases as most patients have large or invasive tumors that cannot be removed completely [4]. Therefore, many patients require subsequent adjunct therapy, particularly medical treatment [5, 6]. Long-acting somatostatin analogs (SSAs) have been widely accepted as the best medical option to treat acromegaly [7]. Nevertheless, at least 35% of patients are considered to be resistant to the commercially available SSAs (Octreotide LAR and Lanreotide autogel) as they do not achieve insulin-like growth factor I (IGF-I) normalization while treated with these drugs [7, 8]. Pegvisomant, a new drug that acts as a growth hormone (GH) receptor antagonist, normalizes IGF-I levels in up to 97% of patients but it does

not induce tumor shrinkage [9, 10]. A potent dopamine agonist, cabergoline, was shown to normalize plasma IGF-I levels in up to 39% of acromegalic patients treated with this drug as monotherapy [11]. Cabergoline efficacy is greater in subjects with concomitant hyperprolactinemia and when the elevation of IGF-I and GH levels is only mild or moderate [8, 11, 12].

There is still limited evidence towards the beneficial effects of adding cabergoline to the medical treatment regimen in acromegalic patients uncontrolled with long-acting SSAs. In four previous studies [13–16], totalizing 81 patients, the rate of IGF-I normalization ranged from 37% to 56% and was not dependent on prolactin (PRL) status (serum PRL levels and immunohistochemical staining for PRL in tumor cells).

The aim of this study was to evaluate the efficacy in normalizing IGF-I levels of the addition of cabergoline to the management of a large cohort of acromegalic patients partially responsive to longterm treatment with the long-acting SSA octreotide LAR (OCT-LAR).

Materials and methods

Patients

Fifty-two acromegalic patients (24 men and 28 women; mean age, 48.4 ± 14.5 years; age range, 23–71), routinely followed in 4 Brazilian neuroendocrine centers, were included in the current study. The main inclusion criteria for this prospective open trial was the persistence of increased IGF-I levels for age despite treatment with OCT-LAR (30 mg intramuscularly [IM]) for at least 12 months. The main exclusion criteria was the presence of optic chiasm compression by the tumor.

Study protocol and assays

The study was performed in accordance with the declaration of Helsinki and was approved by the local ethics committee. All study participants provided informed consent before enrollment had been reached.

The study protocol included the evaluation of the effectiveness of the addition of cabergoline to the medical treatment regimen in acromegalic patients partially responsive to OCT-LAR. The study was divided into three phases:

Phase I: evaluation of the response of IGF-I and GH levels to the short-term cabergoline treatment in addition to OCT-LAR

Cabergoline was given orally at night to the 52 patients for 6 months. The drug was started at the dose of 1.0 mg/week (0.5 mg twice weekly) which was progressively increased by 0.5–1.0 mg every six weeks until normalization of plasma IGF-I levels was obtained, unacceptable side-effects occurred or a maximum dose of 3 mg/week was reached.

Hormonal evaluations (IGF-I, GH, PRL) were performed before the first dose of cabergoline was administered and repeated at 6-week intervals after each cabergoline dose increment.

Phase II: evaluation of the long-term response of IGF-I levels to the addition of cabergoline to OCT-LAR treatment

This part of the study was designed to investigate whether the short-term responses observed in Phase I would be sustained during a long-term follow-up. Thus, all responsive patients were given cabergoline at the lowest doses that normalized their IGF-I levels in Phase I and were followed with clinical and hormonal evaluations at 6-month intervals for at least 12 months. Octreotide and cabergoline doses were kept unchanged during follow-up.

Phase III: evaluation of response of IGF-I levels to cabergoline as monotherapy after long-term combined treatment

This phase of the study was designed to assess whether patients who normalized IGF-I under treatment with cabergoline in addition to OCT-LAR would sustain normal IGF-I levels with cabergoline alone. Thus, after at least 12 months of continuous combined treatment and sustained normalization of IGF-I levels, whenever possible OCT LAR was withdrawn in responsive patients for at least 6 months and IGF-I levels were assessed at 3- to 6-month intervals.

Treatments prior to the addition of cabergoline included transsphenoidal surgery (TSS) and OCT-LAR in 25 patients (48.1%), primary therapy with OCT-LAR in 19 patients (36.5%), and combination of surgery, conventional radiotherapy and OCT-LAR in 8 subjects (15.4%). OCT-LAR was previously administered at a dose of 30 mg every 28 days IM, for a median time of 18 months (range 12–38). TSS and radiotherapy were performed 6–16 years (median, 8 years) and 9 to 14 years (median, 11.5 years), respectively, before the addition of cabergoline.

Patients were assessed clinically and by hormonal determinations every month. Patients who achieved normalization of IGF-I levels after the addition of cabergoline were labeled as responsive whereas those who persisted with increased IGF-I levels were considered non-responsive.

Serum GH levels were measured by a two-site chemiluminescent immunometric assay (Immulite 2000). The sensitivity of this assay is 0.01 ng/ml and the interassay

coefficient of variation was <10%. Serum IGF-I was measured by a solid-phase enzyme labeled chemiluminescent immunometric assay with the sample pre-treatment in an on-bord dilution step (Immulite 2000). The manufacturer's normal range for age was considered. The interassay coefficients of variation were <5%. IGF-I levels are expressed both as absolute values and as a percentage of the upper limit of normal age-matched range (%ULNR-IGF-I; normal: ≤100%). Serum PRL was measured using a two-site chemiluminescent immunometric assay (Immulite 2000). Normal values for PRL, as indicated by the assay method, ranged from 2.0 to 17.0 ng/ml in women and from 2.0 to 15.0 ng/ml in men. The interassay coefficient of variation was less than 5%. Hyperprolactinemia was defined as PRL levels above the normal range.

The radiological study included the evaluation of the sellar region by magnetic resonance imaging (MRI) [Sigma LX GE, Milwaukee, WI], 1.5T, and gradient of 23 mT/m. The slices were axial, coronal, and sagittal in T1, pre- and post-gadolinium, and in T2. The pituitary MRI was performed in all patients prior to the addition of cabergoline to the treatment regimen. Furthermore, in order to investigate the presence or to follow the development of a cardiac valve disease, an echocardiography was performed in 16 patients at study entry and after 6 months of combined treatment as well as in responsive patients every 6 months during the phase II of the study.

The hormonal assays were performed in the same centralized laboratory whereas MRI and ecocardiography were examined by highly skilled specialists in each center involved in the study.

Statistics

For comparison of categorical variables, the chi-squared test or the Fisher exact test were used where appropriate. The Student's *t* test was performed for the comparative analysis of quantitative variables. Results are expressed as percentages and mean values ± SD or unless otherwise indicated. All results were considered significant if two-sided *P* value was less than 0.05.

Results

Characteristics of the patients

At enrollment in the current study, all patients had increased IGF-I levels and the %ULNR-IGF-I ranged from 107.14 to 428.57% (mean ± SD, 222.31 ± 85.20). Random serum GH levels ranged from 2.6 to 35.1 ng/ml (mean ± SD, 7.83 ± 7.11). Hyperprolactinemia with PRL values ranging from 27.9 to 252.8 ng/ml (mean ± SD, 117.80 ± 76.4) was also present in 17 patients (32.7%) (Tables 1, 2).

The immunohistochemical (IHC) features of the tumors were available in only 15 patients previously submitted to TSS. All these adenomas stained positively for GH and 7 of them (46.7%) were also positive for PRL.

At the time of diagnosis, pituitary MRI depicted a macroadenoma (tumor diameter >1 cm) in all patients. Before the addition of cabergoline, pituitary MRI detected macroadenoma remnants in all patients who previously underwent transsphenoidal surgery and intrasellar macroadenomas in 19 patients previously submitted to primary therapy with OCT-LAR (4 of them with parasellar extension). None of the patients had visual field defects.

Efficacy of the short-term combination therapy (octreotide LAR + cabergoline)—phase I of the study

As shown in Table 2, the combination therapy resulted in a significant reduction in mean GH, IGF-I and PRL levels. Mean GH levels decreased from 7.83 ± 7.11 to 4.74 ± 5.51 ng/ml ($P < 0.001$) whereas IGF-I decreased from 584.66 ± 169.58 to 349.73 ± 161.74 ng/ml ($P < 0.001$). After the addition of cabergoline at doses ranging from 1.0 to 3.0 mg/week (mean, 2.19 ± 0.64) normalization of IGF-I levels was achieved in 21 patients (40.4%) whereas in the remaining patients the mean reduction of IGF-I levels was 24.8 ± 19.9% (range, 3.9–56.9). Moreover, safe serum GH levels (GH < 2.5 ng/ml) were observed in 24 patients (46.1%). Finally, both findings (normal IGF-I levels and safe GH levels) were depicted in 15 patients (28.8%). Among responsive patients the final mean %ULNR-IGF-I levels were 57.7 ± 16.7% (range, 24.0–88.44). The corresponding values for non-responsive patients were 175.76 ± 54.51% (range, 111.74–279.54). It should also be noted that no escape phenomenon was observed after cabergoline addition.

PRL levels also changed significantly ($P = 0.001$) during cabergoline treatment, decreasing from 49.51 ± 65.92 to 10.35 ± 12.65 ng/ml. However, serum PRL remained above the normal range (between 25.8 and 71.58 ng/ml) in 3 patients (5.7%) despite the use of cabergoline in doses up to 3 mg/week.

Among responsive patients, the final dose of cabergoline was 1.0 mg/week in 1 (4.7%), 1.5 mg/week in 4 (19.1%), 2.0 mg/week in 9 (42.8%) and 3.0 mg/week in 7 (33.4%). As mentioned, the mean final dose of cabergoline was 2.19 ± 0.64 mg/week.

Efficacy of the long-term combination therapy (octreotide LAR + cabergoline)—phase II of the study

As shown in Fig. 1, all 21 short-term responsive patients sustained normal IGF-I levels during long-term follow-ups

Table 1 Baseline characteristics of the 52 acromegalic patients under octreotide LAR treatment before the addition of cabergoline

No.	Sex	Age (years)	Previous treatment	%ULNR-IGF-I (%)	GH (ng/ml)	PRL (ng/ml)	Residual sellar mass
1	**M**	**23**	**TSS**	**107.14**	**3.2**	**252.3**	**MaR**
2	**F**	**71**	**TSS**	**249.54**	**24.4**	**178.12**	**MaR**
3	**F**	**40**	**TSS**	**167.14**	**3.1**	**190.13**	**MaR**
4	**F**	**31**	**TSS**	**155.66**	**6.3**	**240.12**	**MaR**
5	**M**	**50**	**TSS**	**155.12**	**5.0**	**168.12**	**MaR**
6	**M**	**52**	**TSS**	**232.11**	**6.5**	**214.12**	**MaR**
7	**M**	**54**	**TSS**	**220.0**	**2.7**	**166.0**	**MaR**
8	**F**	**48**	**TSS**	**113.22**	**3.5**	**82.8**	**MaR**
9	**F**	**47**	**TSS**	**179.12**	**3.12**	**12.5**	**MaR**
10	**F**	**46**	**TSS**	**135.56**	**4.2**	**15.0**	**MaR**
11	**F**	**66**	**TSS/RTP/OCT**	**117.12**	**2.6**	**14.2**	**MaR**
12	**F**	**43**	**TSS/RTP/OCT**	**225.23**	**3.8**	**13.2**	**MaR**
13	**M**	**58**	**TSS/RTP/OCT**	**155.14**	**6.5**	**14.12**	**MaR**
14	**M**	**42**	**OCT**	**115.11**	**3.2**	**14.8**	**isMa**
15	**F**	**52**	**OCT**	**118.15**	**2.88**	**15.2**	**isMa**
16	**F**	**54**	**OCT**	**116.12**	**3.0**	**16.3**	**isMa**
17	**F**	**43**	**OCT**	**225.09**	**9.7**	**16.7**	**isMa**
18	**F**	**48**	**OCT**	**143.22**	**5.7**	**15.8**	**isMa**
19	**M**	**29**	**OCT**	**235.12**	**8.0**	**16.8**	**isMa**
20	**M**	**33**	**OCT**	**231.16**	**10.3**	**14.2**	**isMa**
21	**M**	**38**	**OCT**	**232.08**	**8.1**	**13.8**	**isMa**
22	M	55	TSS	117.8	7.3	84.4	MaR
23	M	56	TSS	212.16	16.4	74.5	MaR
24	M	48	TSS	228.13	8.77	45.2	MaR
25	M	49	TSS	224.11	7.8	80.2	MaR
26	M	45	TSS	215.12	4.9	60.5	MaR
27	M	44	TSS	180.08	8.62	42.0	MaR
28	F	42	TSS	145.16	3.0	46.2	MaR
29	F	52	TSS	189.22	3.6	56.8	MaR
30	F	50	TSS	228.02	4.12	76.9	MaR
31	F	45	TSS	192.16	2.9	27.9	MaR
32	F	54	TSS	229.15	4.61	10.2	MaR
33	F	58	TSS	125.32	8.3	18.2	MaR
34	F	38	TSS	222.14	14.4	11.2	MaR
35	M	49	TSS	222.17	5.0	6.5	MaR
36	M	48	TSS	223.28	4.8	14.5	MaR
37	M	44	OCT	428.57	35.1	11.5	isMa
38	M	46	OCT	355.12	13.2	15.6	isMa
39	M	46	OCT	225.14	9.8	9.8	isMa
40	F	52	OCT	412.10	13.6	7.2	isMa
41	F	48	OCT	390.88	8.6	11.8	isMa
42	F	57	OCT	267.09	13.81	13.1	isMa
43	M	33	OCT	233.12	12.1	13.4	isMa
44	F	50	OCT	355.21	9.5	10.6	isMa
45	F	55	OCT	368.33	8.8	14.2	isMa
46	F	38	OCT	225.25	12.2	15.4	isMa
47	F	38	OCT	224.13	10.2	14.8	isMa
48	F	56	OCT	260.12	14.2	13.6	isMa

Table 1 continued

No.	Sex	Age (years)	Previous treatment	%ULNR-IGF-I (%)	GH (ng/ml)	PRL (ng/ml)	Residual sellar mass
49	F	52	OCT	253.33	14.54	13.9	isMa
50	M	59	TSS/RTP/OCT	255.55	15.6	14.8	MaR
51	M	62	TSS/RTP/OCT	252.43	13.5	7.4	MaR
52	M	59	TSS/RTP/OCT	388.12	12.5	7.4	MaR

F female; *M* male; *ULNR* upper limit of normal range; *TSS* transsphenoidal surgery; *OCT* octreotide LAR; *RTP* radiotherapy; *PRL* prolactin; *MaR* macroadenoma remnant; *isMa* intrasellar macroadenoma. Bold lines represent responsive patients. Normal PRL levels: 2.0–17.0 ng/ml in women and 2.0–15.0 ng/ml in men

Table 2 Comparison of hormone levels during treatment with octreotide LAR (OCT-LAR) only and the combination OCT-LAR/cabergoline (CAB)

	OCT-LAR	OCT-LAR + CAB	*P* value
Mean GH levels (ng/ml)	7.83 ± 7.11 (2.6–35.1)	4.74 ± 5.51 (1.2–32.6)	<0.001[a]
Mean IGF-I levels (ng/ml)	584.66 ± 169.58 (397–1020)	349.73 ± 161.74 (170–642)	<0.001[a]
%ULNR IGF-I	222.16 ± 88.15 (107.14–428.57)	132.88 ± 68.87 (34.0–279.54)	<0.001[a]
Hyperprolactinemia	17/52 (32.7%)	3/52 (5.7%)	0.007[b]
Mean PRL levels (ng/ml)	49.51 ± 65.92 (6.51–252.8)	10.35 ± 12.65 (0.79–71.52)	<0.0001[a]

ULNR upper limit of normal range

[a] The student's *t* test

[b] Fischeŕs exact test

ranging from 12 to 24 months (median: 15). Indeed, the final mean %ULNR-IGF-I levels were 57.9 ± 21.2% (range, 23.5–94.37). No escape of treatment was observed during long-term follow-ups.

IGF-I levels after octreotide LAR withdrawal in long-term responders to combined treatment—phase III of the study

The efficacy of cabergoline as monotherapy, after OCT-LAR withdrawal, was assessed in 11 patients who reached normalization of IGF-I levels while on combined therapy. The other patients were kept on OCT-LAR and the reason was heart failure in 3 cases, poorly controlled diabetes mellitus in 4 and patients' refusal in 3 cases. Six months after OCT-LAR withdrawal, IGF-I levels were increased in all patients (mean %ULNR-IGF-I of 148.27 ± 23.54%).

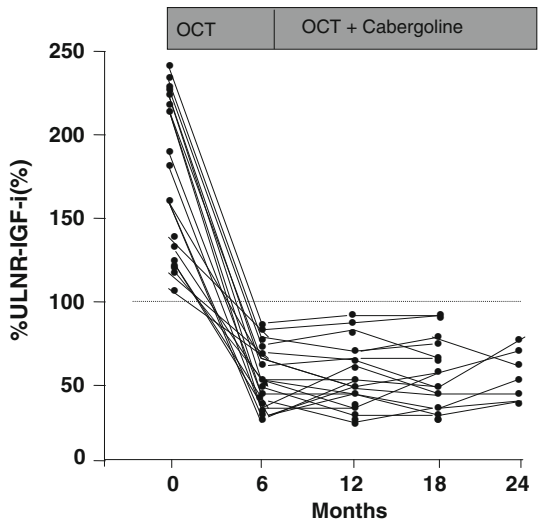

Fig. 1 Behaviour of IGF-I levels in responsive patients during short-term and long-term follow-up under combination treatment (*OCT* octreotide LAR)

Predictors of response to cabergoline addition to octreotide LAR

Compared to non-responsive subjects, responsive patients (the ones who had IGF-I levels normalized) had lower mean %ULNR-IGF-I baseline values (167.39 ± 55.86 vs. 256.39 ± 83.44%; $P < 0.0001$) and lower mean baseline GH levels (5.99 ± 4.94 vs. 10.37 ± 6.16 ng/ml; $P < 0.0001$). Although PRL levels were higher in responsive patients (80.21 ± 90.96 vs. 27.44 ± 28.44 ng/ml; $P < 0.0001$), the rate of hyperprolactinemia did not significantly differ (38.1% vs. 29.0%; $P = 0.4361$) when both groups were compared. Furthermore, the rate of positivity for PRL in immunohistochemical analysis was similar in responsive and non-responsive patients (50.0% vs. 42.8%; $P = 0.5952$) (Table 3).

As shown in Fig. 2, there was a great overlap in IGF-I levels between responsive and non-responsive patients before the addition of cabergoline. However, no patients

Table 3 IGF-I, GH and prolactin (PRL) levels, as well as the rate of positivity for PRL in immunohistochemical analysis, in responsive and non-responsive atients to combined therapy

	Responsive patients	Non-responsive patients	*P* value
%ULNR IGF-I	167.39 ± 55.86 (107.14−249.54)	256.39 ± 83.44 (117.80−428.57)	<0.0001[a]
Mean GH levels (ng/ml)	5.99 ± 4.94 (2.6−24.4)	10.37 ± 6.16 (2.9−35.1)	<0.0001[a]
Hyperprolactinemia	8/21 (38.1%)	9/31 (29.0%)	0.4361[b]
Positive IHC staining for PRL	4/8 (50%)	3/7 (42.8%)	0.5952[b]

ULNR upper limit of normal range

IHC immunohistochemical

[a] The student's *t* test

[b] Fischer's exact test

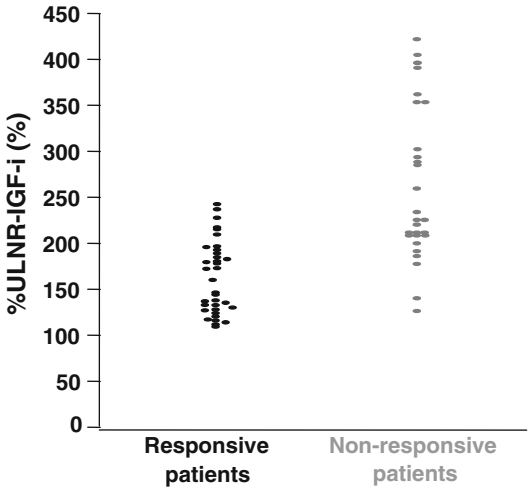

Fig. 2 Comparison of IGF-I levels in responsive and non-responsive patients to combination treatment

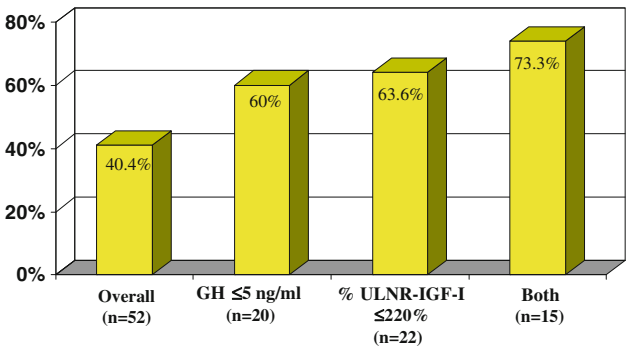

Fig. 3 Rates of IGF-I normalization after the addition of cabergoline according to different criteria

with %ULNR-IGF-I greater than 250% benefited from combined therapy. Moreover, better results concerning normalization of IGF-I levels were found in patients with %ULNR-IGF-I up to 220% (63.6%), in comparison with those with %ULNR-IGF-I ranging from 221 and 250% (38.9%) and the whole group of patients (40.4%). We also found that 12 of the 21 responsive patients (57.1%) had GH levels up to 5 ng/ml. By contrast, 74.2% of non-responsive subjects presented with GH levels >5 ng/ml. Furthermore, among the 20 patients with GH levels up to 5.0 ng/ml, 12 (60%) normalized IGF-I during cabergoline. Finally, the highest rate of IGF-I normalization (73.3%) was found in the subgroup of patients with %ULNR-IGF-I ≤220% and random GH levels ≤5 ng/ml (Fig. 3).

As shown in Table 4, the effectiveness of the addition of cabergoline was apparently not influenced by the type of previous therapy. Indeed, the rate of normalization of IGF-I was 40.0%, 42.1% and 33.1% in patients previously submitted to TSS and OCT-LAR, OCT-LAR primary therapy or the combination of TSS, radiotherapy and OCT-LAR and, respectively.

Tolerability

The combination of cabergoline and OCT-LAR was well tolerated and no patients had to interrupt the treatment. After the addition of cabergoline, transient moderate dizziness and/or nausea were reported in 10 patients (19.2%), whereas 5 patients (9.6%) presented with transient headache. Moreover, none of the patients who underwent echocardiograms developed cardiac valve regurgitation.

Discussion

The dopamine agonist bromocriptine was the first drug used in the management of acromegaly but the results were disappointing and normalization of IGF-I levels was only observed in about 10% of patients, despite the use of very high doses [17]. More recently, some studies, involving about 130 patients, have examined cabergoline therapy for acromegaly and its efficacy varied considerably in these reports [11, 18–21]. In the largest study published to date,

Table 4 The number of responsive patients (with normalization of IGF-I) and non-responsive patients (without normalization of IGF-I) after the addition of cabergoline according to the previous type of therapy

	Group I ($n = 25$)	Group II ($n = 19$)	Group III ($n = 8$)	P value
Responsive patients—n (%)	10 (40)	8 (42.1)	3 (33.3)	0.84[a]
Non-Responsive patients—n (%)	15 (60)	11 (57.9)	5 (66.7)	0.84[a]

Group I: Surgery + Octreotide LAR

Group II: Octreotide LAR only

Group III: Surgery + Radiotherapy + Octreotide LAR

[a] The Chi-squared test

64 unselected patients were treated for up 40 months and the use of cabergoline (at doses ranging 1.0–3.5 mg weekly) resulted in IGF-I normalization in 39% of cases [11]. Better results were found in cases of GH-PRL co-secreting adenomas [11].

The rational for using combination drug therapy in acromegaly is the fact that at least one third of patients are resistant to the treatment with somatostatin analogs (SSAs) which are considered the best medical therapy for the disease [5–7]. In the current study, we observed that the addition of relatively low doses of cabergoline (1.0–3.0 mg/week; mean, 2.19 ± 0.64) to the treatment of acromegalic patients partially responsive to longterm therapy with OCT-LAR was able to induce normalization of IGF-I levels in 40.4% of cases. Moreover, that response was not dependent on the presence of hyperprolactinemia or PRL staining in tumors cells by immunohistochemistry. The best predictors of benefit from combination therapy were IGF-I levels that were significantly lower among responsive patients. Furthermore, no patients with %ULNR-IGF-I >250% normalized IGF-I levels. Normalization of IGF-I levels after the addition of cabergoline was strongly associated with %ULNR-IGF-I ≤ 220% and/or serum random GH levels ≤5.0 ng/ml under octreotide treatment. The efficacy of cabergoline in normalizing IGF-I levels in our study increased progressively according to the criteria adopted to select and analyze patients: 40.4% (overall), 60% (only GH ≤5 ng/ml), 63.6% (only %ULNR-IGF-I ≤220%) and 73.3% (GH ≤5 ng/ml and %ULNR-IGF-I ≤220%). Similar results were reported by Mattar et al. [15] On the other hand, the effectiveness of the addition of cabergoline was not influenced by the type of previous therapy.

In agreement with our results, 4 previous studies [13–16], involving 81 patients, have shown that the rate of IGF-I normalization with combined therapy with OCT-LAR and cabergoline ranged from 37 to 56% and this response was also not influenced by PRL status. The largest of these series evaluated 34 patients with a mean baseline %ULNR-IGF-I of 152 ± 0.62% and found that, using cabergoline doses ranging from 1.5 to 3.5 mg/week (mean, 2.38 ± 1.00), 56% of patients reached normal IGF-I levels [16]. The lowest response rate observed in our study would probably be related to the highest IGF-I levels depicted in our patients (mean %ULNR-IGF-I of 222.31 ± 85.20%). Moreover, we evaluated a larger cohort of patients and our maximal dose of cabergoline was 3.0 mg/week. In these series, as shown in Table 5, patients with baseline %ULNR-IGF-I up to 220% were those who benefited the most from combination treatment. In a large series of acromegalic patients treated with cabergoline alone, pre-treatment IGF-I levels below 750 ng/ml, which roughly corresponds to our cutoff of 220% for the %ULNR IGF-I, were also associated with a better response to cabergoline.

In our protocol, we limited the maximal dose of cabergoline to 3 mg/week as there is evidence that high doses of this drug may be associated with increased risk of cardiac valvular dysfunction, as shown in patients with Parkinson's disease [22]. Moreover, in the series by Colao et al., [23] moderate tricuspide regurgitation without clinical significance was found in patients with prolactinomas chronically treated with cabergoline, particularly those who were given higher doses of cabergoline. However, four other studies showed no differences in valvular abnormalities in patients with hyperprolactinaemia treated with cabergoline compared with controls [24–27]. On the other hand, it has been shown that patients with uncontrolled acromegaly may be at high risk of developing progressive mitral valvular regurgitation [28]. In our study, no valvular cardiac disease was observed in patients treated with cabergoline.

The mechanism underlying the improvement of hormonal response to SSA/cabergoline combined treatment has not been defined yet [16]. Some explanations have been proposed such as a ligand-induced heterodimerization between somatostatin receptors (SSTRs) and the dopamine receptor subtype 2 (D2R) [16]. Indeed, hetero-oligomerizations between SSTRs or between SSTRs and other G protein-coupled receptors, such as D2R, have already been reported [29]. Furthermore, some adenomas expressing D2R and the subtype 2 of SSTRs (SSTR2) show a better inhibition of GH secretion after the addition of cabergoline to SSAs

Table 5 Effectiveness of adding cabergoline (CAB) to medical treatment of acromegalic patients partially responsive to octreotide LAR (data from 5 studies)

Author, year	*N*	Rate of IGF-I normalization		Mean and range of CAB dose	Duration of treatment (months)	Correlation with highPRL levels or positive IHC staining for PRL
		Overall	%ULNR IGF-I $\leq$ 220%			
Cozzi et al. (2004) [13]	19	8 (42%)	7/17 (41%)	2.1 (1.0−3.5)	7.0 ± 4.5	No
Gatta et al. (2005) [14]	9	4 (44%)	6/7 (86%)	1.8 (±0.25 SD)	8.4 ± 4.4	No
Jallad & Bronstein (2009) [16]	34	19 (56%)	18/28 (64%)	1.9 (1.0−3.5)	6.3 ± 3.4	No
Mattar et al. (2010) [15]	19	7 (37%)	7/11 (64%)	2.8 (2.0−3.5)	18.4 ± 5.6	No
Current study	52	21 (40%)	14/22 (64%)	2.1 (1.0-3.0)	18.3 ± 4.4	No
All	133	59 (44%)	52/85 (61%)	–	–	No

* Mean dose

CAB cabergoline; *PRL* prolactin; *IHC* immunohistochemical

treatment [30].Moreover, recently developed chimeric compounds with high affinity for both dopamine and somatostatin receptor subtypes have shown increased GH-suppressing potency as compared to the combination of SSTR and DR subtype-preferential compounds [31–33].

In a previous study, 35% of patients reached normalization of IGF-I levels after increasing the dose of octreotide LAR from 30 to 40 mg monthly [34]. However, in the great majority of studies the maximum dose of octreotide LAR was 30 mg/month [5–7, 13–16, 35–38]. An alternative to OCT-LAR/cabergoline combined therapy would be the combination of OCT-LAR with pegvisomant [39, 40] that is the most effective drug in normalizing plasma IGF-I levels [8–10]. However, pegvisomant is a very expensive drug. Moreover, transient liver enzyme elevations occur in up to one third of patients who receive that treatment regimen [39].

In conclusion, our findings demonstrated that the addition of cabergoline, even at relatively low doses (1.0–3.0 mg/week; mean, 2.19 ± 0.64), is effective in both short- and long-term control of IGF-I levels in acromegalic patients partially responsive to octreotide LAR, particularly in those with mild/moderately elevated GH/IGF-levels, irrespective of prolactin status.

Conflict of interest None.

References

1. Barkan A, Bronstein MD, Bruno OD et al (2010) Management of acromegaly in Latin America: expert panel recommendations. Pituitary 13:168–175
2. Ben-Shlomo A, Melmed S (2008) Acromegaly. Endocrinol Metab Clin North Am 37:101–122
3. Melmed S, Colao A, Barkan A et al (2009) Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 119:3189–3202
4. 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
5. Katznelson L (2008) An update on treatment strategies for acromegaly. Expert Opin Pharmacother 9:2273–2280
6. Melmed S (2009) Acromegaly: pathogenesis and treatment. J Clin Invest 119:3189–3202
7. Ben-Shlomo A, Melmed S (2008) Somatostatin agonists for treatment of acromegaly. Mol Cell Endocrinol 286:192–198
8. Freda PU (2003) How effective are current therapies for acromegaly? Growth Horm IGF Res 13(Suppl A):S144–S151
9. van der Lely AJ, Hutson KR, Trainer PJ et al (2001) Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet 358:1754–1759
10. Colao A, Arnaldi G, Beck-Peccoz P et al (2007) Pegvisomant in acromegaly: why, when, how. J Endocrinol Invest 30:693–699
11. Abs R, Verhelst J, Maiter D et al (1998) Cabergoline in the treatment of acromegaly: a study of 64 patients. J Clin Endocrinol Metab 83:374–378
12. Vilar L, Czepielewski MA, Naves LA et al (2007) Substantial shrinkage of adenomas cosecreting growth hormone and prolactin with use of cabergoline therapy. Endocr Pract 13:396–402
13. 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
14. Gatta B, Hau DH, Catargi B et al (2005) Re-evaluation of the efficacy of the association of cabergoline to somatostatin analogues in acromegalic patients. Clin Endocrinol (Oxf) 63: 477–478
15. Mattar P, Alves Martins MR, Abucham J (2010) Short- and long-term efficacy of combined cabergoline and octreotide treatment in controlling IGF-I levels in acromegaly. Neuroendocrinol 92:120–127
16. Jallad RS, Bronstein MD (2009) Optimizing medical therapy of acromegaly: beneficial effects of cabergoline in patients uncontrolled with long-acting release octreotide. Neuroendocrinol 90:82–92
17. Jaffe CA, Barkan AL (1992) Treatment of acromegaly with dopamine agonists. Endocrinol Metab Clin North Am 21:713–725
18. Cozzi R, Attanasio R, Barausse M et al (1998) Cabergoline in acromegaly: a renewed role for dopamine agonist treatment? Eur J Endocrinol 139:516–521
19. Jackson SNJ, Fowler J, Howlett TA (1997) Cabergoline treatment of acromegaly: a preliminary dose finding study. Clin Endocrinol (Oxf) 46:745–749

20. Muratori M, Arosio M, Gambino G et al (1997) Use of cabergoline in the long-term treatment of hyperprolactinemic and acromegalic patients. J Endocrinol Invest 20:537–546
21. Colao A, Ferone D, Marzullo P et al (1997) Effect of different dopaminergic agents in the treatment of acromegaly. J Clin Endocrinol Metab 82:518–523
22. Zanettini R, Antonini A, Gatto G et al (2007) Valve heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med 356:39–46
23. Colao A, Galderisi M, Di Sarno A et al (2008) Increased prevalence of tricuspid regurgitation in patients with prolactinomas chronically treated with cabergoline. J Clin Endocrinol Metab 93:3777–3784
24. Bogazzi F, Buralli S, Manetti L et al (2008) Treatment with low doses of cabergoline is not associated with increased prevalence of cardiac valve regurgitation in patients with hyperprolactinaemia. Int J Clin Pract 62:1864–1869
25. Vallette S, Serri K, Rivera J et al (2009) Long-term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas. Pituitary 12:153–157
26. Herring N, Szmigielski C, Becher H et al (2009) Valvular heart disease and the use of cabergoline for the treatment of prolactinoma. Clin Endocrinol (Oxf) 70:104–108
27. Nachtigall LB, Valassi E, Lo J et al (2010) Gender effects on cardiac valvular function in hyperprolactinaemic patients receiving cabergoline: a retrospective study. Clin Endocrinol (Oxf) 72:53–58
28. van der Klaauw AA, Bax JJ, Roelfsema F et al (2006) Uncontrolled acromegaly is associated with progressive mitral valvular regurgitation. Growth Horm IGF Res 106:101–107
29. Rocheville M, Lange DC, Kumar U et al (2000) Receptors for dopamine and somatostatin: formation of hetero-oligomers with enhanced functional activity. Science 288:154–157
30. Zatelli MC, Piccin D, Tagliati F et al (2005) Dopamine receptor subtype 2 and somatostatin receptor subtype 5 expression influences somatostatin analogs effects on human somatotroph pituitary adenomas in vitro. J Mol Endocrinol 35:333–341
31. Jaquet P, Gunz G, Saveanu A et al (2005) BIM- 23A760, a chimeric molecule directed towards somatostatin and dopamine receptors, vs. universal somatostatin receptors ligands in GH-secreting pituitary adenomas partial responders to octreotide. J Endocrinol Invest 28(11 Suppl International):21–27
32. Jaquet P, Gunz G, Saveanu A et al (2005) Efficacy of chimeric molecules directed towards multiple somatostatin and dopamine receptors on inhibition of GH and prolactin secretion from GH-secreting pituitary adenomas classified as partially responsive to somatostatinanalog therapy. Eur J Endocrinol 153:135–141
33. Saveanu A, Lavaque GunzG et al (2002) Demonstration of enhanced potency of a chimeric somatostatin-dopamine molecule, BIM- 23A387, in supressing growth hormone and prolactin secretion from human pituitary somatotroph adenoma cells. J Clin Endocrinol Metab 87:5545–5552
34. Colao A, Pivonello R, Auriemma RS et al (2007) Beneficial effect of dose escalation of octreotide-LAR as first-line therapy in patients with acromegaly. Eur J Endocrinol 157:579–587
35. Cozzi R, Attanasio R, Montini M et al (2003) Four-year treatment with octreotide-long-acting repeatable in 110 acromegalic patients: predictive value of short-term results? J Clin Endocrinol Metab 88:3090–3098
36. Jallad RS, Musolino NRC, Salgado L, Bronstein MD (2005) Treatment of acromegaly with octreotide-LAR: extensive experience in a Brazilian institution. Clin Endocrinol (Oxf) 63: 168–175
37. Ben-Shlomo A, Melmed S (2008) Somatostatin agonists for treatment of acromegaly. Mol Cell Endocrinol 286:192–198
38. Freda PU (2002) Somatostatin analogs in acromegaly. J Clin Endocrinol Metab 87:3013–3018
39. Neggers SJ, van Aken MO, Janssen JA et al (2007) Long-term efficacy and safety of combined treatment of somatostatin analogs and pegvisomant in acromegaly. J Clin Endocrinol Metab 92:4598–4601
40. Neggers SJ, van der Lely AJ (2009) Somatostatin analog and pegvisomant combination therapy for acromegaly. Nat Rev Endocrinol 5:546–552