Effective Combination Treatment with Cabergoline and Low-Dose Pegvisomant in Active Acromegaly: A Prospective Clinical Trial

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Context: With adequate dose titration, pegvisomant normalizes IGF-I in up to 97% of patients with acromegaly. Pegvisomant is indicated for treatment-resistant disease but is expensive, particularly at a high dose. It has been used successfully in combination with somatostatin analogs. However, there are no therapeutic reports of pegvisomant in combination with dopamine agonists. Cabergoline is orally active, well-tolerated, and relatively inexpensive, and as monotherapy for acromegaly it is reported to normalize IGF-I in up to 30% of patients.

Objective: The aim of the study was to investigate the efficacy of cabergoline monotherapy and pegvisomant in combination with cabergoline to control serum IGF-I in patients with active acromegaly. Twenty-four patients were recruited into a United Kingdom, multicenter, open-label, prospective clinical trial.

Main Outcome Measure: We measured the change in serum IGF-I.

Results: After 18 wk of dose titration to a maximum dose of 0.5 mg once daily, cabergoline monotherapy did not significantly reduce IGF-I (454 $\pm$ 219 baseline *vs*. 389 $\pm$ 192 ng/ml cabergoline), although two patients did normalize IGF-I. The addition of 10 mg pegvisomant daily for 12 wk significantly reduced IGF-I (389 $\pm$ 192 ng/ml cabergoline *vs*. 229 $\pm$ 101 ng/ml combination), and 68% achieved a normal IGF-I. Twelve weeks after cabergoline withdrawal, while continuing to receive pegvisomant 10 mg, only 26% of patients maintained an IGF-I within the reference range (229 $\pm$ 101 ng/ml combination *vs*. 305 $\pm$ 177 ng/ml pegvisomant). There were no significant changes in liver transaminases or glucose metabolism throughout the study.

Conclusion: These data suggest that combination treatment with cabergoline and pegvisomant is more effective at reducing IGF-I levels than either cabergoline or pegvisomant monotherapy. **(*J Clin Endocrinol Metab* 97: 1187–1193, 2012)**

Pegvisomant is a GH receptor antagonist that has been established as an effective medication for use in patients with treatment-resistant acromegaly. With adequate dose titration, an IGF-I within reference range can be achieved in up to 97% of patients (1). There are accumulating data that efficacy and safety are sustained (2, 3) and that pegvisomant can be used on a once weekly basis (4, 5). The average dose of pegvisomant required to nor-

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Abbreviations: DXA, Dual-energy x-ray absorptiometry; LFT, liver function test; SSA, somatostatin analog; ULN, upper limit of normal.

malize IGF-I is between 15 and 20 mg/d (2, 6, 7), with doses up to 60 mg/d having been used (1, 3). Adequate dose titration with pegvisomant is essential for efficacy, but it is a high-cost medication and that has limited optimal use of the drug (2, 7).

Cabergoline is an ergot-derived dopamine agonist that, according to retrospective studies, normalizes IGF-I in approximately 20–30% of cases and reduces IGF-I and GH levels by 20–30% in patients with acromegaly (8, 9). A recent meta-analysis of cabergoline therapy in acromegaly confirms normalization of IGF-I in 34% of patients (10). Cabergoline is also often used in combination with somatostatin analogs (SSA) with some additional benefit on IGF-I reduction (10–12). However, cabergoline is not licensed for use in acromegaly, and the absence of dose-finding studies and prospective, randomized controlled studies makes it difficult to define its place in the acromegaly treatment algorithm. Cabergoline is a well-tolerated, inexpensive oral medication that can also potentially be used on a weekly basis.

Pegvisomant has been used successfully in combination with SSA to reduce IGF-I levels (13) and improve quality of life parameters (14). An initial study suggested that a combination of pegvisomant and SSA may be more cost-effective than pegvisomant monotherapy (15). However, a recent prospective, controlled trial demonstrated that patients on combination treatment required on average 5 mg less of pegvisomant than patients on pegvisomant monotherapy, implying no financial incentive for combination treatment (16). Furthermore, this combination can be accompanied by deterioration in glucose tolerance (13).

There are no reported studies using a combination of pegvisomant and dopamine agonists. This combination has the potential to be more cost-effective with no deleterious effect on glucose metabolism.

We report a United Kingdom multicenter prospective study investigating the efficacy of combined low-dose pegvisomant and cabergoline in patients with active acromegaly.

Patients and Methods

Patient characteristics

A United Kingdom, five-center, open-label, prospective clinical trial was carried out with ethical and regulatory approval. Patients were identified from the outpatient clinic setting at each center and were sent a patient information sheet outlining the study protocol. Twenty-four patients with acromegaly were enrolled (for characteristics, see Table 1) with the following inclusion criteria: age, over 18 yr; and elevated IGF-I on no treatment or after withdrawal of dopamine agonists (6 wk) or SSA (12 wk). Nineteen patients completed the study.

Protocol

Patients underwent an initial 18-wk cabergoline dose titration phase (Fig. 1). The starting dose of cabergoline (0.5 mg twice weekly) was increased to 1 mg twice weekly at 6 wk if IGF-I

TABLE 1. Baseline characteristics of the 24 patients recruited

Patient no.	Sex	Age (yr)	Year of diagnosis	Tumor size	Prolactin at diagnosis (mU/liter)	Transsphenoidal surgery date	Radiotherapy date	Prior medical therapy	No. of pituitary deficiencies	Study weeks complete
1	F	83	1998	Macro	na	1998	None	O	0	0
2	F	73	1999	Micro	na	2000	None	O + C	0	42
3	F	79	1985	na	na	1985	None	O + C	0	42
4	M	49	1986	Macro	3,950	1986	1989	O	2	42
5	M	62	1982	na	na	1982	1982	C	0	42
6	M	39	2006	Macro	46,000	2006	None	C	3	4
7	F	21	2006	Macro	na	2006	None	O + C	2	42
8	M	53	1988	Micro	na	1988	None	None	0	42
9	M	68	1976	Micro	244	1976	1976	C	1	42
10	F	70	1998	Micro	1,897	None	None	C	0	42
11	M	44	1992	Macro	255	1992	1993	C	0	42
12	M	47	2006	Macro	124	2006	None	None	0	42
13	F	51	2006	Macro	527	2006	None	None	0	16
14	M	49	2007	Macro	83	2007	None	None	0	42
15	M	57	2007	Macro	1,087	2007	None	None	0	34
16	M	67	2000	Micro	189	2002	2002	O + L	0	42
17	F	46	2006	Macro	125	2007 × 2	None	None	0	42
18	M	49	na	na	na	na	na	na	na	16
19	M	43	1998	Macro	493	1998	1999	O	0	42
20	M	51	1993	Macro	1,123	1993	1994	O	0	42
21	F	54	2001	Macro	365	2003	None	O	0	42
22	M	43	2004	Macro	174	2005	None	O + C	0	42
23	F	62	2007	Macro	329	2007	None	None	0	42
24	M	70	2000	Micro	148	None	None	C	0	42

M, Male; F, female; O, octreotide; C, cabergoline; L, lanreotide; na, data not available.

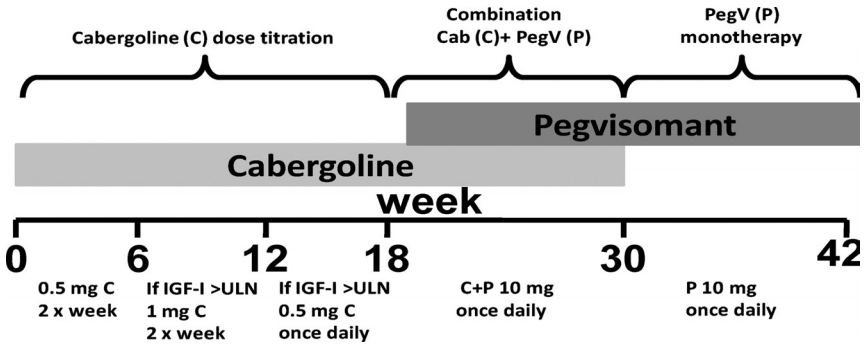

FIG. 1. Study protocol.

remained elevated. This was further increased to 0.5 mg once daily if IGF-I was still raised at 12 wk. At 18 wk, patients had 10 mg/d of pegvisomant added to their ongoing cabergoline treatment. Cabergoline was stopped at 30 wk, and a 12-wk period of pegvisomant monotherapy at 10 mg once daily followed. A dual-energy x-ray absorptiometry (DXA) body composition scan was performed at wk 0 and 42. The primary outcome measures were differences in IGF-I levels.

IGF-I, GH, glucose, glycosylated hemoglobin, prolactin, and lipids were measured at wk 0, 4, 10, 18, 30, and 42. Every 4 wk vital signs, fasting glucose, and liver function tests (LFT) (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatise, and gamma-glutamyl transferase) were monitored, and an AcroQol (17) questionnaire was completed. At wk 0, 18, 30, and 42, an oral glucose tolerance test was carried out.

Prospective decisions on cabergoline dose titration during the study were based on centrally measured IGF-I; however, to minimize batch to batch variation, the data presented are from a final reanalysis of all samples in a single batch. GH and pegvisomant were analyzed as a single batch at the end of the study.

Assays

IGF-I levels

Serum IGF-I levels were measured using an Immulite-2000 solid-phase enzyme-labeled chemiluminescent immunometric assay (Siemens, Los Angeles, CA). Within-assay variability was 6.4, 2.9, and 2.6% at low (mean, 45.6 ± 2.9 ng/ml), medium (mean, 238 ± 6.9 ng/ml), and high (mean, 550 ± 14.5 ng/ml) serum IGF-I values, respectively. The age-related IGF-I reference range was based on 1499 samples analyzed on the Siemens Immulite assay from a healthy adult population (18).

Pegvisomant drug level

Serum concentrations of pegvisomant were determined by an immunofluorometric sandwich type assay previously described (19). Within-assay variability was 7.5, 4.6, and 5.2% at concentrations of 160, 650, and 3900 ng/ml, respectively. The between-assay variability was 13.5, 6.4, and 8.5% at the same concentrations.

Growth hormone

Serum concentrations of GH were determined using a specific GH assay designed to exclude interference from pegvisomant. This assay has been previously described in detail (20, 21). Intraassay variability was 4.1 and 3.9% at concentrations of 5.2 and 14.6 ng/ml, respectively. Interassay variability at the same concentrations was 7.3 and 9.2%, respectively.

Prolactin, LFT, lipids, and glucose

Serum prolactin concentrations were determined using a two-site immunoassay (ADVIA centaur XP immunoassay system, Siemens, Surrey, UK).

Plasma glucose was measured using the glucose oxidase method, and LFT, total cholesterol, high-density lipoprotein, and triglycerides were measured by the automated ADVIA system (ADIVA 1800 Chemistry system, Siemens).

DXA scans

Where available, patients underwent a DXA whole body composition scan (Hologic Discovery A; Hologic Inc., Bedford, MA) at their local center at wk 0 and 42.

Statistical analysis

Serum IGF-I is expressed as an absolute concentration (nanograms per milliliter) and also as a percentage of the upper limit of normal (ULN) for the age-related reference range. For the purpose of statistical comparison using SPSS (SPSS Statistics Version 19, IBM, UK), IGF-I, GH, and prolactin have been log-transformed to better satisfy normality assumptions. Longitudinal data were compared using repeated measures-ANOVA. Results were considered significant if $P < 0.05$. Bonferroni *post hoc* analysis was used to compare the groups, and results were considered significant if $P < 0.008$.

Results

Nineteen patients completed the study. Two patients withdrew for lack of perceived benefit, one patient developed abnormal LFT on cabergoline alone (see *Adverse events*), and two patients developed moderate depressive symptoms on cabergoline monotherapy.

IGF-I levels

Cabergoline dose titration over 18 wk did not lead to a significant reduction in IGF-I [mean IGF-I, 454 ± 219 ng/ml (1.8 ± 0.7 × ULN) at baseline *vs.* 389 ± 192 ng/ml (1.6 ± 0.4 × ULN) at 18 wk], although two patients (11%) achieved an IGF-I within the reference range on 0.5 mg/d (Fig. 2).

At wk 30, after 12-wk treatment with the combination of cabergoline and low-dose pegvisomant (10 mg once daily), IGF-I had fallen significantly [mean IGF-I, 229 ± 101 ng/ml (0.95 ± 0.4 × ULN); $P < 0.001$], with 13 patients (68%) achieving an IGF-I within the reference range.

After withdrawal of cabergoline, 12 wk of pegvisomant monotherapy led to a significant increase in IGF-I levels

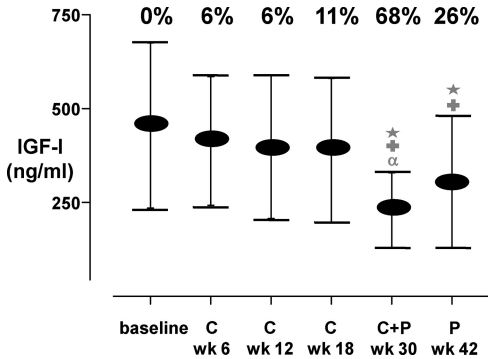

FIG. 2. Line plot to illustrate mean ± SD of IGF-I levels (ng/ml) at each time point during the trial. Percentages are the percentage of patients achieving an IGF-I within the reference range at each time point. C, Cabergoline; P, pegvisomant. α, $P < 0.008$ *vs.* wk 42; ★, $P < 0.008$ *vs.* baseline; ✚, $P < 0.008$ *vs.* wk 18.

[wk 42 mean IGF-I, 305 ± 177 ng/ml (1.2 ± 0.5 × ULN); $P = 0.002$], with only five patients (26%) maintaining an IGF-I within the reference range (Table 2).

GH and pegvisomant concentrations

GH levels after cabergoline monotherapy or combination therapy were unchanged compared with baseline (6.7 ± 12.5 ng/ml at baseline *vs.* 2.6 ± 2.3 ng/ml at 18 wk and 7.1 ± 8.6 ng/ml at 30 wk). Removal of cabergoline led to an increase in GH levels (11.9 ± 18.5 ng/ml) such that they were significantly higher than at baseline ($P = 0.006$) or on cabergoline monotherapy ($P = 0.002$).

There was no significant difference between mean serum pegvisomant concentrations with the different treatments [3811 ± 4888 ng/ml (cabergoline + pegvisomant) *vs.* 3484 ± 4877 ng/ml (pegvisomant)] (Fig. 3). Two patients had undetectable serum pegvisomant levels at wk 42. Both of these also had low levels at wk 30 (129 and 456 ng/ml), and one patient had a serum pegvisomant concentration 14-fold higher at wk 42 compared with wk 30, raising the possibility of poor compliance. Reanalysis of all parameters with these three patients being excluded did not alter the significance of any results.

Serum prolactin

Only one patient had serum prolactin above the reference range at baseline (2264 mU/liter; reference range, 45–619 mU/liter). This patient achieved an IGF-I within reference range with cabergoline treatment alone, and prolactin decreased to 295 mU/liter on 0.5 mg/d at 18 wk.

Overall serum prolactin concentrations were significantly reduced at wk 18 after cabergoline dose titration [median (range), 52.5 (0–2264) mU/liter at baseline *vs.* 2.5 (0–295) mU/liter at wk 18; $P = 0.001$]. Prolactin concentrations were unchanged after 12 wk of pegvisomant

TABLE 2. Individual IGF-I levels (ng/ml) at each study time point for the 19 patients completing the study and weekly cabergoline dose achieved

Patient no.	Baseline IGF-I (ng/ml)	Wk 18 IGF-I (C) (ng/ml)	Wk 18 dose of cabergoline/wk (mg)	Wk 30 IGF-I (C + P) (ng/ml)	Wk 42 IGF-I (P) (ng/ml)	IGF-I ULN reference range (ng/ml)
2	275	235	3.5	232	240	188
3	350	377	3.5	269	273	177
4	347	360	3.5	189	194	252
5	361	273	3.5	176	315	225
7	906	577	2	378	892	582
8	309	263[a]	1	225	296	238
9	203	261	3.5	91.1	110	200
10	227	253	3.5	182	203	200
11	297	235	2	231	298	267
12	866	1051	3.5	399	312	267
14	567	364	3.5	199	503	252
16	292	366	3.5	289	330	212
17	628	378	3.5	85.9	152	267
19	541	390	3.5	364	393	267
20	314	313	3.5	207	189	252
21	581	393	3.5	179	286	238
22	768	533	3.5	216	327	267
23	234	229	3.5	54.2	69.8	215
24	563	543	3.5	397	415	200
Mean	454	389		229	305	
SD	220	192		101	177	

C, Cabergoline; P, pegvisomant.

[a] This patient did not achieve a maximal dose of cabergoline because during prospective measurement of IGF-I during the cabergoline titration phase the result was within the reference range. After retrospective batch reanalysis of the IGF-I samples, this was measured at just above the reference range.

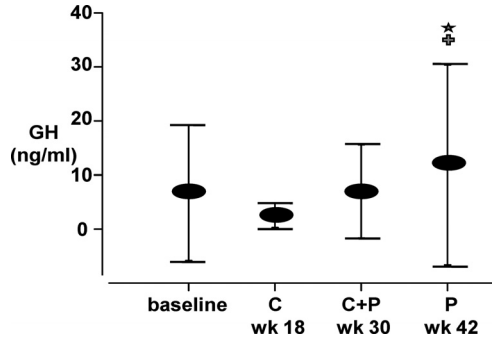

FIG. 3. Line plot to illustrate mean ± SD of GH levels (ng/ml) at wk 0, 18, 30, and 42. C, Cabergoline; P, pegvisomant. ⋆, $P < 0.008$ *vs.* wk 0; ✚, $P < 0.008$ *vs.* wk 18.

and cabergoline combination [2 (0–690) mU/liter], but withdrawal of cabergoline at wk 30 did lead to a significant increase in serum prolactin at 42 wk [13 (1–991) mU/liter; $P < 0.001$], although this did not return to baseline levels.

Metabolic factors and body composition

There was a small but significant increase in weight with combination treatment (93 ± 24 at wk 30 *vs.* 91 ± 22 kg at baseline; $P < 0.05$).

Overall there was no significant difference in glucose or lipid profile across the different treatment regimens (Table 3). However, at baseline seven patients were categorized as having impaired glucose tolerance or diabetes mellitus by oral glucose tolerance test, compared with three on cabergoline alone, three on combination treatment, and four on pegvisomant alone. Eight patients had DXA body composition scans. There were no significant differences in total fat or lean mass or percentage fat after the treatment protocol.

Quality of life

Assessment of quality of life using the AcroQol questionnaire did not demonstrate any difference across the treatment groups [AcroQol score, 69 ± 17 (wk 0), 71 ± 18 (wk 18), 72 ± 18 (wk 30), and 74 ± 18 (wk 42)].

Adverse events

Serious adverse events

One patient developed abnormal LFT during treatment with 1 mg cabergoline twice weekly, leading to withdrawal from the study. The LFT abnormalities were predominantly raised transaminases occurring 1 month after elective laparoscopic cholecystectomy for gallstone disease. The abnormality was felt to be related to postoperative treatment with antibiotics and resolved 1 month after withdrawal of the antibiotics and cabergoline. Another patient developed a lower respiratory tract infection at wk 40, which necessitated admission to hospital overnight. Neither serious adverse event was felt to be related to the study medications.

Discussion

This study is the first prospective trial of cabergoline use in acromegaly, and it demonstrates an IGF-I normalization rate of 11% at 18 wk using a maximum dose of 3.5 mg/wk with no overall significant reduction in IGF-I. The combination of low-dose pegvisomant and cabergoline resulted in a significantly lower IGF-I than either cabergoline or pegvisomant monotherapy, with 68% achieving a normal IGF-I.

The first large retrospective study of cabergoline treatment in acromegaly demonstrated normalization of IGF-I in 39% of patients taking up to 3.5 mg/wk (8). In that study, predictors of normalization of IGF-I included a lower IGF-I at baseline and cosecretion with prolactin. Similar rates of IGF-I normalization (33%) were seen in a more recent prospective audit of 15 patients with active acromegaly (9), although these patients had an overall lower IGF-I at baseline and there was no correlation between prolactin cosecretion and response. Similarly, a larger analysis of 172 patients from a United Kingdom acromegaly database showed no correlation between response to dopamine agonists and prolactin levels, although previous radiotherapy did improve the response (22). A recent meta-analysis including the above stud-

TABLE 3. Metabolic and quality of life parameters throughout the study

Parameter	Baseline (wk 0)	C (wk 18)	C + P (wk 30)	P (wk 42)
Total cholesterol	4.9 ± 1.3	4.6 ± 0.8	4.9 ± 0.9	4.9 ± 0.7
HDL-cholesterol	1.3 ± 0.4	1.4 ± 0.4	1.4 ± 0.5	1.3 ± 0.4
Triglycerides	1.9 ± 2.1	1.4 ± 0.9	1.6 ± 1.1	1.6 ± 0.8
Weight (kg)	91 ± 22	93 ± 23	93 ± 24[a]	93 ± 24
Glycosylated hemoglobin (%)	5.7 ± 0.6	5.5 ± 0.4	5.5 ± 0.4	5.7 ± 0.5
Fasting plasma glucose (mmol/liter)	5.3 ± 0.8	4.9 ± 0.5	5.4 ± 0.9	5.4 ± 0.9
2-h glucose during OGTT (mmol/liter)	7.2 ± 3.8	5.0 ± 2.1[a]	6.4 ± 3.5	6.3 ± 2.8
AcroQol	69 ± 17	71 ± 18	72 ± 18	74 ± 18

Data are expressed as mean ± SD. HDL, High-density lipoprotein; OGTT, oral glucose tolerance test; C, cabergoline; P, pegvisomant.

[a] $P < 0.05$ compared to baseline.

ies confirms an overall improved response to cabergoline in those with a lower baseline IGF-I and raised baseline prolactin (10).

The prospective results with cabergoline monotherapy presented here show a much lower IGF-I normalization rate, with only two (11%) patients achieving a normal IGF-I with up to 3.5 mg/wk. The baseline IGF-I level (454 ± 219 ng/ml) was similar to that described by Moyes *et al.* (9) (479 ng/ml), although different IGF-I assays were employed. In our prospective study, there was only a 15% decrease in IGF-I at wk 18 compared with baseline. One explanation is that the patients in the current study may have been more treatment resistant. Furthermore, successful dose titration above 3.5 mg/wk has been reported, with recent data suggesting that cabergoline doses of up to 12 mg/wk for the treatment of prolactinomas were associated with a reduction in prolactin levels (23). Whether this is true for somatotroph adenomas is unclear. The use of higher doses of cabergoline needs to be approached with some caution in view of concerns regarding an increased incidence of cardiac valvular defects in patients with Parkinson's disease treated with large cumulative doses of ergot-derived dopamine agonists (24, 25).

The characteristics of the two patients who achieved control with cabergoline monotherapy in our study differ considerably. The first had a relatively modest elevation of IGF-I at baseline (292 ng/ml, equivalent to 1.3 × ULN) with a prolactin concentration in the normal range. The second was a young female with a tumor cosecreting GH and prolactin. Her IGF-I was 906 ng/ml (1.7 × ULN) at baseline with a prolactin level of 2264 mU/liter. She attained an IGF-I within reference range (577 ng/ml), and prolactin fell to 295 mU/liter on 3.5 mg of cabergoline per week. Interestingly, in this patient, withdrawal of cabergoline and treatment with 10 mg pegvisomant alone led to a dramatic increase in her IGF-I (892 ng/ml). There are clearly wide variations in individual tumor sensitivity to dopamine agonists. However, it appears that, despite overall data reported to the contrary, in selected patients who cosecrete prolactin or have modest IGF-I elevations, cabergoline can be a very effective monotherapy.

Addition of low-dose pegvisomant (10 mg/d) to cabergoline resulted in a 40% reduction in serum IGF-I, with 13 (68%) patients achieving an IGF-I within reference range on this combination. The defining trials with pegvisomant monotherapy demonstrated approximately 50% normalization of IGF-I on 10 mg once daily, with up to 97% achieving a normal IGF-I with dose titration up to 40 mg/d (1).

Stopping cabergoline at wk 30 led to an increase in IGF-I in 18 patients, with only five (26%) having an IGF-I within the reference range at wk 42 on pegvisomant 10 mg once daily monotherapy. Within a clinical setting of dose titration during pegvisomant monotherapy, an IGF-I above the reference range should lead to an increase in the dose of pegvisomant. By implication, the combination of pegvisomant and cabergoline may allow the use of lower doses of pegvisomant, potentially cutting treatment cost.

Two patients had very low serum pegvisomant levels on combination therapy, and these dropped to undetectable on pegvisomant monotherapy. The reasons for this are unknown, but a lack of compliance must be considered. However, exclusion of these two patients from the analysis did not change the significance of the results. Reasons for wide variations in serum pegvisomant levels are not well understood but have been demonstrated previously (26) and require further studies.

A major determinant of pegvisomant dose requirements is pretreatment GH levels (27). The fact that GH levels rose after stopping cabergoline therapy and that this was associated with a lower number of patients with an IGF-I within reference range is consistent with the notion that GH levels may predict the response to pegvisomant.

Previous studies have described the successful use of combination therapy with SSA and pegvisomant. Feenstra *et al.* (28) demonstrated normalization of IGF-I in 90% of patients uncontrolled on SSA therapy with the addition of pegvisomant at a mean dose of 80 mg/wk. This combination also had the advantage of inducing tumor shrinkage and reducing GH levels (29). However, there was an increased risk of diabetes mellitus secondary to the negative effect of SSA on insulin secretion and of abnormalities in LFT, particularly in those with diabetes (16, 30). In contrast to these results, our data show no detrimental effect of cabergoline and pegvisomant cotreatment on glucose or lipid metabolism, with some indication that these were improved, as would be expected with reduced GH levels and GH receptor blockade. Furthermore, there were no significant changes in LFT over the study period.

The combination of cabergoline and low-dose pegvisomant treatment is more effective at reducing IGF-I than either cabergoline or low-dose pegvisomant monotherapy (10 mg). In comparison with the coadministration of pegvisomant with SSA, the combination described here has several advantages: cabergoline is well-tolerated, orally administered, and less expensive than SSA. Both cabergoline and pegvisomant have the potential to be given on a twice or once weekly basis. Furthermore, combined use may reduce the need for pegvisomant dose escalation, significantly reducing the cost of effectively treating acromegaly.

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