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Treatment with Growth Hormone Receptor Antagonist in Acromegaly: Effect on Cardiac Structure and Performance

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Aim: The aim of the current study was to evaluate the effect of short-term (6 months) and long-term (18 months) treatment with pegvisomant on cardiac structure and performance in patients with acromegaly.

Patients: Seventeen patients (nine women, eight men, 27–61 yr) with active acromegaly entered and 12 completed the long-term study. After a baseline evaluation, including measurement of hemodynamic, biochemical, and hormonal parameters, and a standard Doppler echocardiography, treatment with pegvisomant was started at the initial dose of 10 mg/d, increasing by 5 mg/d every 6 wk on the basis of IGF-I levels until normalization or the achievement of a maximal dose of 40 mg/d.

Results: After short-term treatment, IGF-I levels were normalized in 10 of the 17 (59%) patients. Left ventricular mass index (LVMi) was significantly decreased without changes in diastolic and systolic performance. After long-term treatment, IGF-I levels were normalized in 10 of the 12 (83%) patients. Blood glucose and serum insulin levels were decreased compared with baseline. LVMi was further decreased compared with short-term treatment, so that the prevalence of left ventricle hypertrophy decreased from 50% at baseline to 17% after 18 months of treatment. Moreover, ejection fraction as well as early to late (atrial) peak velocity ratio (E/A) were significantly increased, whereas isovolumic relaxation time was significantly decreased compared with baseline, demonstrating an improvement of both diastolic and systolic function. A significant correlation was found between the change in IGF-I levels and that of left ventricular ejection fraction. In general, the prevalence of cardiac insufficiency was present in 13 of the 17 (76%) patients at baseline and in one (8%) patient after 18 months of treatment.

Conclusions: Long-term treatment with the GH receptor antagonist improves acromegalic cardiomyopathy by decreasing cardiac hypertrophy and enhancing diastolic and systolic function, and consequently partially or completely reverting the cardiac insufficiency. (***J Clin Endocrinol Metab* 92: 476–482, 2007**)

ACROMEGALY IS ASSOCIATED with a specific cardiomyopathy, characterized by biventricular hypertrophy complicated by initial diastolic dysfunction and late systolic dysfunction, progressively worsening until heart failure (1). GH and IGF-I excess are responsible for most of the cardiac damage although systemic arterial hypertension, glucose intolerance, and dyslipidemia associated with the disease contribute to acromegalic cardiomyopathy (2). Control of GH and IGF-I levels, induced by the surgical removal of the GH-secreting pituitary tumor or by medical therapy with somatostatin analogs, has been demonstrated to improve clinical and metabolic abnormalities as well as cardiac structure and performance, by reducing the biventricular hypertrophy and ameliorating (or at least arresting the progression of) diastolic and systolic dysfunction (1, 2). At least one third of patients with acromegaly are not cured by surgery and not controlled by medical therapy with somatostatin analogs, maintaining persistently increased GH and IGF-I levels and thus being exposed to worsening of cardiac performance (3, 4).

The treatment options for acromegaly have been enriched recently by the inclusion of a genetically engineered GH-receptor antagonist, namely pegvisomant, which blocks the dimerization of GH receptor, thereby inducing inhibition of IGF-I production (5). Pegvisomant has been demonstrated to normalize IGF-I levels in more than 90% of patients with active acromegaly (6) and in approximately 80% of patients unsuccessfully treated by surgery and/or resistant to medical treatment with somatostatin analogs (7). The treatment is accompanied by a significant improvement of clinical and metabolic abnormalities. It is noteworthy that pegvisomant does not act on the pituitary tumor. Therefore, the lowering of IGF-I levels is associated with an increase of GH levels during the period of treatment.

We have reported recently that normalization of IGF-I levels by pegvisomant treatment in patients with acromegaly resistant to previous surgery and long-term high-dose somatostatin analogs induces a reduction of diastolic blood pressure in hypertensive patients and improves glucose me-

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Abbreviations: BMI, Body mass index; EF, ejection fraction; hGH, human GH; IGFBP, IGF binding protein; IVRT, isovolumic relaxation time; IVST, interventricular septum thickness; LV, left ventricle; LVM, LV mass; LVMi, LVM index; LVPWT, LV posterior wall thickness; NYHA, New York Heart Association.

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tabolism in those with glucose intolerance or diabetes (7). The aim of this open, prospective study was to evaluate the effect of short-term and long-term treatment with pegvisomant on cardiac structure and performance by echocardiography.

Patients and Methods

Inclusion and exclusion criteria

This open-label 18-month study included patients 18 yr of age or older with a previously established diagnosis of acromegaly (GH nadir during an oral glucose tolerance test > 1 μg/liter). IGF-I levels at least 1.3 times above the upper limit of normal age- and sex-matched controls after a 4-month wash-out of long-acting somatostatin analogs was an inclusion criterion. The patients should have had stable hormone replacement therapy for hypopituitarism for at least 6 months before study start, and stable size of the pituitary tumor for the last 12 months as documented by magnetic resonance imaging. Patients were excluded from the study if they had treatment with dopamine agonists for the last 5 wk before study start, a pituitary adenoma with a distance from the optic chiasm of 3 mm or less; chronic hepatitis, known or suspected drug/alcohol abuse, or other conditions such as severe hepatic or renal disease or malnutrition, that could result in abnormal GH or IGF-I concentrations; had a history of relevant drug or food allergies; or if they were not willing or were unable to self-administer the study medication. All women of childbearing age were required to use an acceptable form of contraception throughout the study. Women who were pregnant or nursing were excluded from participation. The Ethical Committee of the University "Federico II" of Naples approved the protocol, and all patients provided written informed consent before study participation.

Patients

Seventeen patients (nine women, eight men, age range 27–61 yr, median 48 yr) were enrolled in this study. All but three patients had previously undergone surgery, and two patients had received radiotherapy after an unsuccessful neurosurgical operation. Fourteen of the 17 patients had been treated with somatostatin analogs (octreotide LAR 40 mg/month or lanreotide 120 mg/month) for at least 6 months (mean: 6.1 $\pm$ 4.8 yr) without achieving disease control. Among the remaining three patients, who did not have medical treatment before the study, two had disease relapse after an apparently successful surgery performed several years before, whereas the remaining patient entered the study immediately after diagnosis. At baseline, nine (50%) patients had systemic arterial hypertension and were treated with diuretics (3), angiotensin converting enzyme-inhibitors (1), angiotensin receptor antagonist (3), calcio-antagonists (2), β-blockers (1), and/or saline restriction (4). Four patients (23.5%) had diabetes mellitus, whereas six (35.3%) patients had impaired glucose tolerance; both the two patients with diabetes mellitus and the three patients with impaired glucose tolerance were in dietary treatment. Nine patients (52.9%) had a clear-cut LV hypertrophy, 10 (58.8%) had a LV diastolic dysfunction, and two (11.8%) had a LV systolic dysfunction. Considering the New York Heart Association (NYHA) classification of cardiac insufficiency, 10 (58.8%) patients were classified in class I (asymptomatic left ventricular dysfunction), two (11.8%) patients in class II (mild limitation of physical activity after effort), and one (5.9%) patient in class III (marked limitation of the activity after effort). During the study, five patients dropped out: three patients because of poor compliance with the drug at 4-yr follow-up, one patient because of liver function test abnormality at 6-months follow-up, and one patient because of progressive increase of tumor size at 1-yr follow-up.

The patient profile is shown in Table 1. Patients no. 2, 10, 14, 15, and 16 dropped out before the completion of the study. All but three (nos. 2, 11, and 14 of Table 1) patients of the present study were described in a previous paper, where clinical, biochemical, and radiological parameters were considered but cardiac structure and performance were not evaluated.

Study design

After the baseline evaluation, all patients started the 18-month treatment with pegvisomant. During the study, clinical parameters, including height, weight, and body mass index (BMI), and hemodynamic parameters, including heart rate, systolic and diastolic blood pressure were registered at baseline and every 6 wk. Biochemical parameters including fasting serum glucose and insulin, serum triglycerides, cholesterol, and fibrinogen, were measured at baseline and every 6 months. Hormonal parameters, including serum GH and IGF-I levels, were evaluated every 6 wk. A Doppler echocardiography was performed at baseline and every 6 months for the entire period of the study to evaluate cardiac structure and performance. This study evaluated three points: baseline, the short-term (6 months), and the long-term (18 months) period of treatment with pegvisomant. The short-term evaluation considered all 17 patients, whereas the long-term evaluation considered the 12 patients who completed the study.

Treatment protocol

After an initial loading dose of 40 mg pegvisomant, treatment was started with 10 mg/d sc. The dose was adjusted ($\pm$ 5 mg) every 6 wk based on IGF-I levels obtained 2 wk before the time for dose adjustment.

TABLE 1. Profile of patients at study entry

Patients			Serum GH levels (μg/liter)	Serum IGF-I levels (μg/liter)	Magnetic resonance imaging findings	Previous treatments	Pegvisomant treatment	
No.	Sex/age (yr)	Dose (mg/d)					Duration (months)	Side effects
1	F/46	18.6	728	Remnant at r-CS	S, SS	15	18	
2	F/52	7.7	756	Remnant at r-CS	S	25	6	
3	M/52	9.3	900	Remnant posterior	SS	35	18	
4	F/58	8.5	674	Empty sella	S, SS	25	18	
5	F/49	48.5	638	Remnant at r-CS	S, R, SS	25	18	
6	M/42	74.8	870	Residual macro I, Ss, bilateral P	S, SS	40	18	Increase of tumor size
7	F/55	17.2	729	Residual macro I, r-P	S, SS	20	18	
8	M/29	3.4	748	Remnant at l-CS	S, SS	25	18	Increase of transaminases
9	F/39	71.2	834	Residual macro I, r-P	S, SS	40	18	
10	M/61	15	935	Residual macro i, l-P	S, R, SS	25	6	
11	F/48	71.2	378	Micro		15	18	
12	M/28	9	898	Remnant at r-CS	S, SS	25	18	
13	F/44	4.5	525	Remnant at r-CS	S, SS	15	18	
14	M/66	6.5	445	Negative	S	10	6	Cholestasis
15	M/32	14.4	756	Residual macro I, r-P	S, SS	15	12	Increase of tumor size
16	M/52	21.9	1023	Negative	SS	40	9	
17	F/35	5.6	594	Negative	S, SS	10	18	

S, Surgery; R, radiotherapy; SS, somatostatin analogs; CS, cavernous sinus; Ss, suprasellar; I, intrasellar; P, parasellar; i, infrasellar; r, right; l, left; F, female; M, male.

The goal was to obtain an IGF-I concentration within the normal range for sex and age, taking 5 mg/d as the minimal dose and 40 mg/d as the maximal dose.

Assays

Before and during pegvisomant treatment, IGF-I assays were performed at the Neuroendocrine Unit laboratories, Ludwig Maximilians University of Munich. Serum samples were shipped frozen on dry ice. Before analysis, samples were thawed and allowed to reach ambient temperature. IGF-I levels were measured by the automated Advantage chemiluminescent IGF-I assay system (Nichols Diagnostics Institute, Bad Nauheim, Germany). For this method, samples are acidified to separate IGF-I from its binding protein IGF binding protein (IGFBP) 3. To prevent reassociation of IGF-I and IGFBPs, and thus to exclude interference of IGFBP-3, the acidified samples are incubated with an excess of IGF-II. The intraassay coefficients of variation were 11.5, 5.1, and 3.5% at concentrations of 42, 262, and 522 ng/ml, respectively. At the same concentrations, the between assay coefficients of variation were 10.6, 10.6, and 10.2%. The lower limit of quantification was 17 ng/ml, the linear range was 17–1000 ng/ml. To monitor endogenous human GH (hGH) secretion in patients treated with the hGH-analog pegvisomant, a specific assay was designed to be free of interference by the drug. From a panel of monoclonal antibodies raised against hGH, a pair of antibodies was identified targeting epitopes in receptor binding site 1 and 2, respectively, which have been mutated in the hGH-analog. Neither of the monoclonal antibodies selected showed cross-reaction with pegvisomant, indicating that they target amino acid residues mutated in pegvisomant. Combining these antibodies (named 8B11 and 6C1) in a sandwich assay leads to a linear dose relationship for hGH with a lower detection limit of 0.2 ng/ml and an upper end of the linear working range at 50 ng/ml for 50-μl samples. WHO IRP 80/505 is used as the calibrator. Intraassay variability was 4.1 and 3.9% at concentrations of 5.2 and 14.6 μg/liter, respectively. Interassay variability at the same concentrations was determined to be 7.3 and 9.2%, respectively.

Doppler echocardiography

Standard Doppler echocardiography was performed by Vingmed system 5 (GE, Horten, Norway), using a 2.5 MHz transducer during three to five consecutive cardiac cycles. Doppler-echo tracings were recorded on super VHS videotapes and high-fidelity paper strip at a velocity of 50–100 mm/sec. All measurements were analyzed by two experienced sonographers, unaware of clinical and laboratory data. Echocardiographic quantitative analyses of left ventricle (LV) were performed in the parasternal long-axis view according to the standards of our laboratory (8). LV posterior wall thickness (LVPWT) and interventricular septum thickness (IVST) were measured during the diastolic phase of the cardiac cycle, particularly at the end diastole, *i.e.* at the onset of the ECG QRS complex. LV mass (LVM) was calculated by the Devereux formula (9). LVM index (LVMi) was obtained by dividing LVM by body surface area. LV ejection fraction (EF) was calculated on the basis of the following formula: (LVEDV − LVESV)/LVEDV × 100, where LVEDV = LV end-diastolic volume and LVESV = LV end-systolic volume. Pulsed Doppler assessment of mitral inflow was performed in apical four-chamber view, with the sample volume placed at the tips levels. The following measurements of LV diastolic function were determined: early (E) to late or atrial (A) peak velocities ratio, the E/A, and isovolumic relaxation time (IVRT), taken as the time interval occurring between the end of LV systolic output flow and the onset of transmitral E velocity, by placing the sample volume between outflow tract and the mitral valve. LV hypertrophy was defined when LVMi was 135 g/m^2 or more in men and 110 mg/m^2 or more in women. LV diastolic dysfunction was defined when E/A was lower than 1 or 0.5 for patients younger or older than 50 yr, respectively, and/or IVRT was longer than 92 (<30 yr of age), 100 (30–50 yr of age), or 105 msec (>50 yr of age). LV systolic dysfunction was defined when EF was lower than 50%.

Statistical analysis

The statistical analysis was performed by means of SPSS Inc. (Cary, NC) package. The effect of pegvisomant was analyzed by nonparametric test using Wilcoxon test. The comparison between the prevalence of the different parameters before and after pegvisomant was performed by χ^2 test corrected by Fisher exact test if necessary. The correlation study was performed by linear regression analysis calculating the Pearson's coefficient. Data are reported as mean ± SD unless otherwise specified. Significance was set at 5%.

Results

Short-term (6 months) treatment with pegvisomant

Effect on clinical, hemodynamic, biochemical, and hormonal parameters (Table 2). At a mean dose of 20.3 ± 5.7 and median dose of 25 mg/d (two patients with 10 mg, four with 15 mg, two with 20 mg, and nine with 25 mg/d), IGF-I levels were decreased from 731 ± 176 to 434 ± 224 μg/liter ($P < 0.0001$) and normalized in 10 (59%) of the 17 patients. Conversely, GH levels were increased. No significant difference was found in BMI, heart rate, blood pressure, serum cholesterol, triglycerides, or fibrinogen levels. A slight but not significant decrease of serum glucose ($P = 0.06$) was accompanied by stable serum insulin levels ($P = 0.46$). No significant difference was found in the prevalence of systemic arterial hypertension and impairment of glucose tolerance.

Effect on cardiac performance (Table 3). LVM ($P = 0.007$) and LVMi ($P < 0.0001$) were decreased compared with baseline as well as the LVPWT and IVST. These parameters were improved both in patients who normalized ($P = 0.005$) and in those who did not normalize ($P = 0.043$) IGF-I levels. A higher, although not significant, reduction in LVMi was found in patients who normalized than in those who did not normalize IGF-I levels (ΔLVMi = −10.0 *vs.* −3.8, $P = 0.055$; Fig. 1). No significant difference was found in left ventricular EF, E/A, and IVRT either in the whole population or in those who did normalize IGF-I levels. No significant difference was found in the prevalence of LV hypertrophy and dysfunction. Indeed, the prevalence of LV hypertrophy passed from 52.9% at baseline to 35.3%, due to the normalization of LV mass in three patients, who normalized IGF-I levels. The prevalence of LV diastolic dysfunction passed from 58.8 to 41.2%, whereas the prevalence of LV systolic dysfunction passed from 11.8 to 17.6%. The patient with NYHA class III cardiac insufficiency were reclassified in NYHA class II.

TABLE 2. Effect of 6-month pegvisomant treatment on clinical, hormonal, hemodynamic, and biochemical parameters in 17 patients with acromegaly

Parameters	Before	6 Months	*P*
BMI (kg/m^2)	29.0 ± 3.7	29.2 ± 3.6	0.20
IGF-I (μg/liter)	731.4 ± 175.8	257.1 ± 107.5	<0.001
GH (μg/liter)	19.8 ± 22.7	44.7 ± 41.1	<0.001
Heart rate (bpm)	72.2 ± 8.0	71.8 ± 9.1	0.76
Systolic blood pressure (mm Hg)	133.2 ± 16.3	129.1 ± 12.1	0.20
Diastolic blood pressure (mm Hg)	86.5 ± 13.1	86.5 ± 9.5	0.75
Blood glucose (mg/dl)	100.5 ± 21.3	94.2 ± 17.6	0.06
Serum insulin (mU/liter)	11.6 ± 6.3	10.3 ± 3.3	0.46
Serum cholesterol (mg/dl)	212.2 ± 41.2	220.4 ± 31.6	0.16
Serum triglycerides (mg/dl)	132.9 ± 69.0	143.2 ± 57.7	0.52
Serum fibrinogen (mg/dl)	333.0 ± 71.4	339.3 ± 70.9	0.75

TABLE 3. Effect of 6-month pegvisomant treatment on echocardiographic parameters in 17 patients with acromegaly

Parameters	Before	6 Months	*P*
LVM (g)	239.7 ± 57.5	231.7 ± 54.6	0.007
LVMi (g/m^2)	128.9 ± 28.2	121.4 ± 30.1	<0.001
LVPWT (mm)	10.7 ± 1.2	10.4 ± 1.3	0.006
IVST (mm)	12.4 ± 2.3	12.1 ± 2.1	0.011
EF (%)	58.7 ± 8.0	61.7 ± 10.9	0.29
E/A	1.03 ± 0.3	1.01 ± 0.3	0.42
IVRT (sec)	97.5 ± 13.8	95.6 ± 15.2	0.20

Long-term (18 months) treatment with pegvisomant

Effect on clinical, hemodynamic, biochemical, and hormonal parameters (Table 4). At the mean dose of 24.2 ± 10.0 and median dose of 25 mg/d (one patient with 10 mg, three with 15 mg, one with 20 mg, four with 25 mg, one with 35 mg, and 2 with 40 mg/d), IGF-I levels were decreased from 710 ± 159 μg/liter at baseline to 220 ± 92 μg/liter at last follow-up (P = 0.002); IGF-I levels were normalized in 10 (83%) of the 12 patients, and strongly reduced but still above the normal range in two (17%) patients. GH levels were further increased. No significant difference compared with baseline was found in BMI, serum cholesterol, triglycerides, and fibrinogen levels and heart rate; systolic and diastolic blood pressure were slightly but not significantly decreased. Blood glucose (P = 0.026) and serum insulin levels (P = 0.028) were decreased compared with baseline. No difference was found in the prevalence (from 50 to 41.7%) of systemic arterial hypertension, although a reduction of the dose or number of the antihypertensive drugs was possible in three patients and withdrawal of antihypertensive treatment was possible in the only patient who became normotensive. Conversely, the prevalence of diabetes mellitus and impaired glucose tolerance passed from 25 and 16.7% to 0 and 8.3% due to the normalization of glucose profile in the two patients with initial impaired glucose tolerance and in two of the three patients with initial diabetes mellitus; dietary treatment was continued in the only patient with persistent impaired glucose tolerance.

Effect on cardiac performance (Table 5). LVM (P = 0.006) and LVMi (P = 0.003) were reduced compared with baseline, showing a progressive decrease of cardiac mass during the entire period of treatment. Both LVPWT and IVST were significantly decreased compared with baseline. Left ventricular EF (P = 0.041) as well as E/A (P = 0.015) were increased, whereas IVRT (P = 0.012) was decreased compared with baseline evaluation. The individual and median changes in LVMi and EF between baseline and 18-month evaluation are shown in Fig. 2. A correlation was found between the change in IGF-I levels and that of left ventricular EF (r = 0.81, P = 0.001, Fig. 3). No significant correlation was found between the change in IGF-I levels and that in LVMi, as well as in LV E/A, or IVRT. The prevalence of LV hypertrophy passed from 50.0% at baseline to 16.7%, due to the normalization of LV mass in four of the six patients with LV hypertrophy at baseline. The prevalence of LV diastolic dysfunction passed from 58.3 to 8.3% (χ^2 = 4.688, P = 0.03), whereas the prevalence of LV systolic dysfunction passed from 8.3 to 0%. No clear-cut cardiac insufficiency was found in any patients except one, who was classified in NYHA class I.

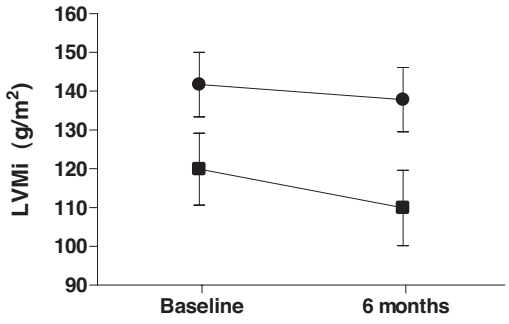

FIG. 1. LVMi before and after 6 months of treatment with pegvisomant in patients with acromegaly who normalized (■) or did not normalize (●) IGF-I levels. The values are expressed as mean ± SE.

TABLE 4. Effect of 18-month pegvisomant treatment on clinical, hormonal, hemodynamic, and biochemical parameters in 12 patients with acromegaly

Parameters	Before	18 Months	*P*
BMI (kg/m^2)	29.4 ± 4.1	29.0 ± 3.0	0.94
IGF-I (μg/liter)	709.7 ± 159.2	219.7 ± 92.0	0.002
GH (μg/liter)	22.6 ± 26.6	61.2 ± 75.6	0.002
Heart rate (bpm)	72.7 ± 6.7	74.8 ± 9.2	0.40
Systolic blood pressure (mm Hg)	131.7 ± 14.7	128.3 ± 21.7	0.30
Diastolic blood pressure (mm Hg)	87.5 ± 13.2	81.2 ± 11.7	0.18
Blood glucose (mg/dl)	100.9 ± 24.3	88.1 ± 13.1	0.026
Serum insulin (mU/liter)	12.5 ± 7.2	8.2 ± 2.8	0.028
Serum cholesterol (mg/dl)	214.9 ± 44.0	217.4 ± 39.9	0.64
Serum triglycerides (mg/dl)	120.7 ± 45.2	118.5 ± 36.1	0.84
Serum fibrinogen (mg/dl)	324.9 ± 69.0	320.0 ± 70.2	0.58

Discussion

The results of the current study demonstrate that, in patients with active acromegaly, treatment with the GH receptor antagonist pegvisomant, by inducing normalization of IGF-I secretion, is able to reverse LV hypertrophy despite long-standing disease activity, and also improves the LV diastolic and systolic performance progressively. These effects have an important clinical impact because the cardiac insufficiency occurring in the majority of these patients before starting pegvisomant treatment was partially or completely reversed after long-term treatment.

Acromegaly is known to be associated with a specific cardiomyopathy, mainly characterized by biventricular hypertrophy and subsequent impairment of diastolic and systolic function (1, 2). The pathogenesis of acromegalic cardio-

TABLE 5. Effect of 18-month pegvisomant treatment on echocardiographic parameters in 12 patients with acromegaly

Parameters	Before	18 Months	*P*
LVM (g)	226.5 ± 60.8	203.9 ± 52.5	0.006
LVMi (g/m^2)	123.3 ± 28.4	107.2 ± 25.5	0.003
LVPWT (mm)	10.5 ± 1.1	9.7 ± 1.2	0.005
IVST (mm)	11.8 ± 1.4	11.0 ± 1.4	0.031
EF (%)	59.3 ± 5.8	63.4 ± 7.2	0.041
E/A	1.07 ± 0.3	1.27 ± 0.3	0.015
IVRT (sec)	97.1 ± 14.9	88.0 ± 12.1	0.012

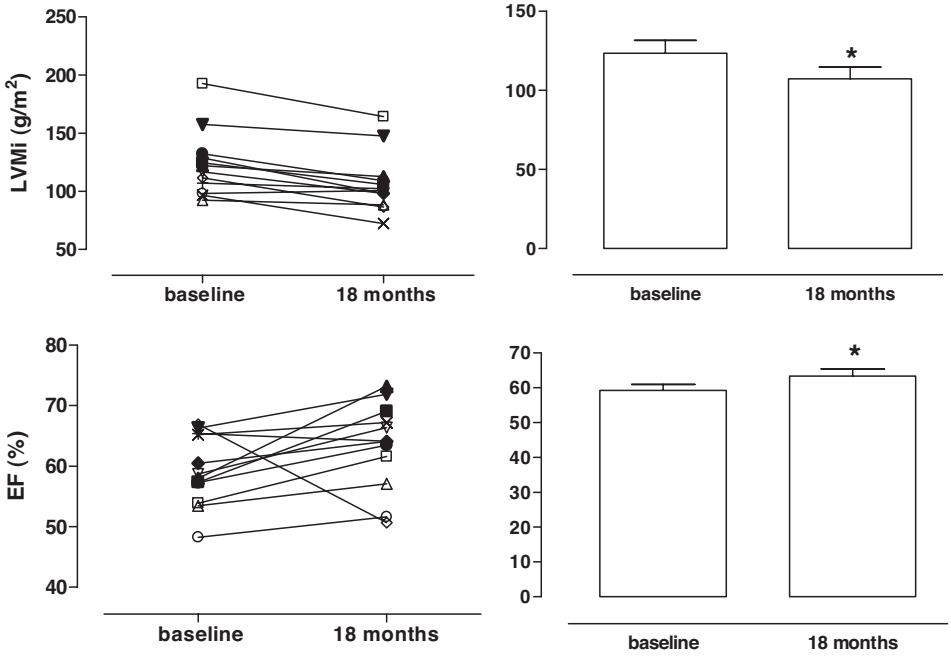

FIG. 2. LVMi (*top*) and left ventricular EF (*bottom*) as single values (*left*) and as mean ± SE (*right*) in 12 patients with acromegaly at baseline and after 6 and 18 months of treatment with pegvisomant. *, $P < 0.05$.

myopathy includes either a direct action of GH and IGF-I on the heart, or indirect mechanisms by which GH and IGF-I induce hypertension and glucose intolerance with consequent increased cardiovascular risk and cardiac remodeling (10, 11). The role of both GH and IGF-I in determining a direct change in cardiac muscle is supported by evidence mainly collected in animal models. GH or IGF-I receptors are expressed and IGF-I is synthesized in cardiomyocytes (12–14). In animal models, either GH or IGF-I increases myocardial contractility likely via an increased calcium responsiveness of the myocardium, and induces a hypertrophic response of the heart (15–17).

LV hypertrophy is found in most patients with acromegaly at diagnosis, in particular in those with a long disease history, as demonstrated by different method of calculation (18), and interstitial fibrosis constitutes the main abnormality at histology (19). LV hypertrophy is significantly increased from young to elderly patients (1), suggesting that it is an early event in acromegaly, which worsens with the duration of disease. Hypertension and glucose intolerance are likely the most important factors aggravating acromegalic cardiomyopathy, because the prevalence of LV hypertrophy was found to be higher in patients with these metabolic complications (20). The most striking functional disturbance of early acromegalic cardiomyopathy is inadequate ventricular filling capacity, as demonstrated by the decrease of E/A and the prolongation of the IVRT, which characterize a diastolic dysfunction (1, 21). In the presence of diastolic dysfunction, incomplete recovery of an adequate preload can affect systolic function, especially during physical exercise (1, 21). Diastolic and systolic dysfunction are less frequent than LV hypertrophy, being observed in less than half and one third of patients, respectively (1).

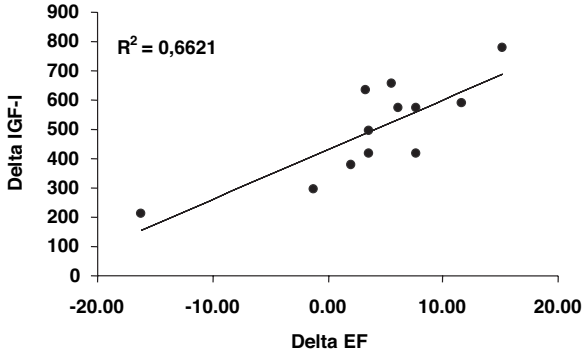

FIG. 3. Correlation between the difference (Δ) between baseline and 18-month follow-up of IGF-I and left ventricular EF.

Normalization of GH and IGF-I levels has been demonstrated to improve or at least to arrest the progression of acromegalic cardiomyopathy. In particular, medical treatment with somatostatin analogs has been reported to successfully improve cardiovascular parameters and cardiomyopathy. A rapid reduction of LV hypertrophy occurs in patients treated with short-lasting and long-lasting formulation of octreotide and lanreotide (22, 23). The effect on the cardiac mass is more evident after 1 yr of treatment, and is reported to be followed by improvement of diastolic and systolic performance (24). The achievement of biochemical control of the disease is mandatory to improve diastolic and systolic function (25). In fact, systolic function at exercise improved only in the patients achieving disease control and not in those who did not, even if in all patients LV hypertrophy reduced (26). Persistence of active acromegaly has been shown to be associated with further impairment of cardiac performance (24). Recovery from LV hypertrophy or dysfunction appears to depend, however, not only on the strict hormonal control of acromegaly but also on the control of the concomitant clinical and metabolic complications, as well as the age of the patients and the duration of GH and IGF-I hypersecretion before intervention (27). Treatment with somatostatin analogs is well tolerated but is efficacious

in inducing disease remission with normalization of GH and IGF-I levels in about 50% of unselected patients with acromegaly.

The GH receptor antagonist, pegvisomant, represents a novel therapeutic approach for patients with acromegaly, acting by blocking the GH receptor dimerizaton and consequently IGF-I production and seems to have more advantageous effects on glucose metabolism compared with somatostatin analogs (28). Pegvisomant treatment is reported to normalize IGF-I levels in the majority of patients with acromegaly. Long-term treatment with pegvisomant normalizes IGF-I levels in more than 90% of patients with acromegaly (6) and around 80% of patients with acromegaly resistant to somatostatin analogs (7). The current study has focused attention on the ability of pegvisomant to improve cardiomyopathy in acromegalic patients. The results of this open prospective study demonstrated that 6-months treatment with pegvisomant was able to significantly reduce LVM but not improve LV diastolic and systolic performance. At the 6-month follow-up, despite being significantly decreased, serum IGF-I levels were normalized in less than 60% of patients. After 18 months of treatment at a higher dose, IGF-I was normalized in more than 80% of the patients. LVM was consistently reduced compared with baseline and further reduced compared with the short-term evaluation. In addition, a significant improvement of diastolic performance, measured as an increase of E/A and a shortening of IVRT, and systolic performance, measured as an increase in EF, was observed as well. The more marked effect on the heart at 18 months compared with 6 months was mainly explained by the higher percentage of patients with normal IGF-I at the last examination. However, an additional effect of the treatment over time contributed to the evident reduction of cardiac mass. The changes in IGF-I levels were correlated with those in systolic performance but not with those in LVM or diastolic performance. This seems to suggest that the degree of IGF-I decrease parallels the improvement of cardiac function more than that of cardiac mass. An alternative hypothesis is that several factors beyond IGF-I excess might contribute to the occurrence of LV hypertrophy and impairment of diastolic performance, whereas IGF-I has a major role in determining impairment of systolic function.

In conclusion, long-term treatment with the GH receptor antagonist pegvisomant for 18 months improves cardiomyopathy in patients with acromegaly by decreasing cardiac hypertrophy and enhancing diastolic and systolic performance, preventing the development or the progression of cardiac insufficiency.

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Erratum

In the article "Atherogenic Lipoprotein Phenotype and Low-Density Lipoproteins Size and Subclasses in Women with Polycystic Ovary Syndrome" by Kaspar Berneis, Manfredi Rizzo, Veronica Lazzaroni, Franca Fruzzetti, and Enrico Carmina (*The Journal of Clinical Endocrinology & Metabolism* **92:**186–189, 2007), the authors report a misspelling of the third author's name, which is Veronica Lazzarini. *The authors regret the error.*