0021-972X/99/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 84, No. 2
Printed in U.S.A.

Cardiac Effects of Slow-Release Lanreotide, a Slow-Release Somatostatin Analog, in Acromegalic Patients*

ROBERTO BALDELLI, ELISABETTA FERRETTI, MARIE-LISE JAFFRAIN-REA, GIANLUCA IACOBELLIS, GIUSEPPE MINNITI, BARBARA CARACCIOLO, CARLO MORONI, ROSARIO CASSONE, ALBERTO GULINO, AND GUIDO TAMBURRANO

Departments of Endocrinology (R.B., G.I., G.M., B.C., G.T.), Internal Medicine (C.M., R.C.), and Experimental Medicine and Pathology (A.G.), University of Rome "La Sapienza", 00161 Rome, Italy; and Department of Experimental Medicine (E.F., M.-L.J.-R.), University of L'Aquila, L'Aquila, Italy

ABSTRACT

Cardiac involvement, mostly characterized by left ventricular hypertrophy associated with various degrees of cardiac dysfunction, greatly contributes to the increased mortality and morbidity observed in acromegaly. Lanreotide is a new SRIF analog characterized by a slow-release (SR) formulation with the peculiarity of a 30-mg im administration every 10–14 days. In this study, 13 patients with postoperative active acromegaly (9 females, 4 males, 45.9 ± 16.3 yr old) underwent an echo-Doppler and hormonal study before and during a 12-month period of treatment with SR-lanreotide. GH and insulin-like growth factor I plasma levels (mean ± SD) decreased significantly throughout the study period (from 10.1 ± 2.2 to 3.9 ± 0.9 ng/mL for GH, $P < 0.005$; and from 511.0 ± 33.0 to 305.0 ± 34.2 ng/mL for insulin-like growth factor I, $P < 0.0001$). Left ventricular mass index (mean ± SD, 137.1 ± 7.5 g/m^2 at baseline) decreased after 3 months (120.0 ± 5.4 g/m^2), 6 months (111.7 ± 5.7 g/m^2), and 12 months (110.3 ± 5.2 g/m^2) of treatment ($P < 0.005$ at each time-point). This reduction in left ventricular mass index was accompanied by an improvement in some indexes of left ventricular diastolic function, especially the isovolumetric relaxation time (mean ± SD, 109.1 ± 4.6 m/sec at baseline), which decreased after 3 months (91.9 ± 2.8 m/sec), 6 months (92.3 ± 3.2 m/sec), and 12 months (92.2 ± 3.0 m/sec) of treatment ($P < 0.005$ at each time-point). We conclude that SR-lanreotide is able to improve cardiac morphology and functional abnormalities in acromegaly; whether such beneficial effects on cardiac parameters will contribute to improve life expectancy in these patients should be further investigated. (*J Clin Endocrinol Metab* **84:** 527–532, 1999)

CARDIOVASCULAR involvement represents the major cause of death in patients with acromegaly. Left ventricular hypertrophy (LVH) occurs in up to 70% of the patients (1–3) [in part, because of direct effects of GH/insulin-like growth factor-I (IGF-I) hypersecretion on the heart] and can be associated with various degrees of cardiac dysfunction, ranging from impaired diastolic filling to overt cardiac failure (4–6). Hypertension, coronary diseases, valvular disorders, diabetes, and dyslipidemia can contribute to the increased incidence of cardiovascular diseases in these patients. Among the broad spectrum of long-term systemic complications of the acromegalic disease, cardiovascular abnormalities were initially considered to be among the less reversible after treatment (7, 8), although some beneficial effects on systemic hypertension, which represents a significant additional risk factor for the development of LVH in these patients (9), have been observed (10). However, during the last 10 yr, a significant improvement of cardiac mass and function has been reported after successful treatment of acromegaly by either surgery (11, 12) or medical treatment with octreotide (13–17).

To avoid the inconvenience of multiple daily injections in long-term octreotide therapy, new SRIF analogs with slow-release (SR) formulations have been synthesized. Lanreotide (Ipsen Laboratories), an SR formulation of the SRIF analog BIM 23014 (18–21) requiring an im injection every 10 to 14 days, has recently become available in Italy. The effects of SR-lanreotide on GH and IGF-I hypersecretion have been shown to be rather similar to those of octreotide (22). To our knowledge, no data concerning the influence of such a treatment on cardiac parameters in acromegaly are available to date. Thus, an open prospective study has been designed in order to evaluate the effects a 12-months treatment period in a series of 13 patients with persistent active disease after surgery. Ventricular structure and function have been studied by echo-Doppler examination at different time-points during the treatment period, including a short term evaluation after a single injection of SR-lanreotide.

Materials and Methods

Patients

Thirteen patients with active acromegaly (four males, nine females, 45.9 ± 16.3 yr old) were included in the study, the mean duration of the disease being clinically evaluated about 12.1 ± 4.5 yr. None of them had overt diabetes, and three suffered from mild hypertension, according to the definition of the World Health Organization/International Society of Hypertension (23); the mean value of three measurements was considered for each subject, and hypertension was defined as systolic blood pressure (SBP) more than 140 mm Hg and/or diastolic blood pressure more than 90 mm Hg. Acromegalic patients with specific cardiac diseases (such as valvular dysfunction, ischemic heart disease, primary

Received July 28, 1998. Revised October 20, 1998. Accepted October 26, 1998.

Address all correspondence and requests for reprints to: Roberto Baldelli, M.D., Clinica Medica II - Dipartimento di Endocrinologia, Università "La Sapienza", Viale del Policlinico, 00161 Rome, Italy.

* This work was presented, in part, at the 79th Annual Meeting of The Endocrine Society in Minneapolis (Abstract P3–47); it was supported, in part, by Grant 9706151106 from MURST and by CISD, Rome, Italy.

cardiomyopathy, specific myocardial diseases, or severe hypertension) were excluded from the study after a careful patient's interview, physical examination, 12-lead electrocardiogram, chest x-ray, and complete echo-Doppler evaluation at baseline. The individual characteristics of the selected patients are listed in Table 1. In brief, all patients had been previously operated on by a transphenoidal route, followed in two cases by a transcranial route because of grossly invasive, giant adenomas at the time of diagnosis. Seven patients had also received a conventional postoperative radiotherapy 2.0 ± 1.9 yr before the study. Nine patients had been previously treated for 2.6 ± 2.5 yr with octreotide and/or cabergoline, which were withdrawn for at least 6 weeks before they entered the study. The evolutivity of the disease at the time of the study was attested by several random GH levels more than 2.5 ng/mL, not suppressible less than 1 ng/mL after a 75-g glucose tolerance test, and accompanied by elevated age-corrected IGF-I plasma levels. Evidence for residual pituitary adenoma tissue, mainly intrasellar in most cases, was confirmed in all patients by computerized tomography and/or nuclear magnetic resonance imaging. In two patients, anterior pituitary dysfunction was adequately compensated for by L-T_4, cortisone acetate, and/or gonadal steroids replacement therapy before entering the study. All patients gave their informed consent to the study.

Study design

All patients initially received SR-lanreotide (30 mg im) every 14 days over a 3-month period. In patients with persisting high levels of GH (>2.5 ng/mL) and/or elevated age-corrected IGF-I levels at the end of the first trimester, SR-lanreotide was subsequently administered every 10 days for the rest of the study period (n = 10). The time-points of the study were defined as follows: T0: pretreatment evaluation; T1: 10 days after the first im injection of 30 mg SR-lanreotide; T2: 14 days after the first im injection of 30 mg SR-lanreotide; T3: after 3 months of treatment (SR-lanreotide, 30 mg every 14 days); T4: after 6 months of treatment (SR-lanreotide, 30 mg every 10–14 days); and T5: after 12 months of treatment (SR-lanreotide, 30 mg every 10–14 days).

Fasting GH and IGF-I values and echo-Doppler studies were assessed at each time-point, with the exception of the echo-Doppler study, which was not performed at T1. To evaluate the possible contribution of previous radiotherapy on GH and IGF-I improvement throughout the study period, these parameters were also determined after 1 month withdrawal of SR-lanreotide in irradiated patients but were not statistically different from the prestudy values (8.9 ± 2.2 *vs.* 12.1 ± 4.0 ng/mL for GH, P = not significant; 552.8 ± 41.0 *vs.* 493.2 ± 52.0 ng/mL for IGF-I, P = not significant), indicating that GH/IGF-I decrease during the study period was mainly caused by SR-lanreotide treatment.

Thirteen healthy age- and sex-matched subjects were also studied as a control group.

Hormonal assays

Basal pituitary function was routinely assessed by measuring fasting PRL, FT_4, FT_3, TSH, FSH, LH, testosterone, and/or estradiol, cortisol, ACTH, and dehydroepiandrosterone-sulfate by commercially available kits. Plasma GH was determined by immunoradiometric assay (Biodata Diagnostics, Rome, Italy), with a detection limit of 0.1 ng/mL; the inter- and intraassay coefficients of variations ranged from 2.38–2.87 and from 2.17–2.54%, respectively. Plasma IGF-I was determined by RIA after acid-ethanol extraction (BioChem ImmunoSystems, Italy); inter-and intraassay coefficients of variation ranged from 5.9–7.1% and from 3.4–5.4%, respectively. The following age-corrected IGF-I were considered normal: ≤483 ng/mL (20–30 yr), ≤397 ng/mL (31–40 yr), ≤306 ng/mL (41–50 yr), and ≤249 ng/mL (>50 yr).

M-B mode echo-Doppler studies

M-B mode echo-Doppler studies were carried out using a Vingmed CFM 800 Unit. The examination and the analysis of the results were performed by a single operator, who was unaware of the endocrinological status of the patient; the studies were conducted according to the American Society of Echocardiography directions and worldwide-used routine standards (24), as previously reported (25).

Briefly, left ventricular diameter and septal and posterior wall thickness were measured at end diastole and end systole, as defined by the electrocardiographic tracing. Left ventricular mass (LVM) was estimated using the anatomically validated formula of Devereux and Reicheck, according to the Penn convention (26, 27). The LVM index (LVMI) was determined by the ratio of LVM to body surface area. LVH was defined by LVMI exceeding 134 g/m^2 in men and 110 g/m^2 in women, respectively (27).

Left ventricular systolic function was evaluated by fractional shortening (FS), ejection fraction, stroke volume (SV), and left ventricular end-systolic stress (ESS). SV represents the difference between end-diastolic and end-systolic left ventricular volumes and was used to calculate the cardiac output (CO) according to the following formula: CO = heart rate (beats/min) × SV. In addition, two dynamic parameters were also considered: 1) left ventricular ESS (taking into account the systolic blood pressure at the time of the study) was calculated according to the formula of Reicheck: ESS (10^3 dynes/m^2) = 0.334 × SBP × LVESD/PWST (1 + PWST/LVESD), where SBP is the systolic blood pressure, PWST is the posterior wall thickness, LVESD is the left ventricular end systolic diameter; and 2) the frequency-corrected mean velocity of circumferential fraction (MVCFc) was calculated using the following formula: MVCFc = FS/ETc, where ETc is the frequency, corrected for left ventricular ejection time, calculated using the formula: ETc = (ET)/R-R (interval from electrocardiogram).

Diastolic function was evaluated by the following pulsed Doppler echocardiographic parameters: 1) the isovolumetric relaxation time (IRT), an index of ventricular relaxation properties; and 2) early (E) and late (A) transmitral peak flow velocities, as well as E/A ratio, indicating the pattern of ventricular diastolic filling. IRT was measured by placing the doppler beam between the mitral and aortic valve junction and represents the interval between the end of aortic valve closure and onset of peak flow velocities and the mitral valve opening. E and A peak flow

TABLE 1. Characteristics of patients before the study

Pt	Age	Sex	DD	BMI	HY	GH (ng/mL)	IGF-I (ng/mL)	PT	NS	RT	RxT[a]
1	21	F	6	32	no	2.2	420	OCT/CAB	TC/TS	L-T_4, GS, C	6 months
2	26	M	7	33	no	6.4	706	no	TS		
3	31	M	10	33	no	5.5	533	CAB	TS		
4	33	F	10	20	no	21.6	407	OCT	TS		2 yr
5	36	F	11	36	no	2.3	662	OCT	TS	L-T_4, GS	1 yr
6	39	F	11	23	no	30.0	550	no	TS		1 yr
7	42	F	9	43	yes	7.3	671	no	TS		6 months
8	55	F	15	30	no	8.6	444	OCT	TS		
9	56	F	16	28	no	6.3	310	OCT	TS		5 yr
10	60	F	15	23	no	15.0	432	OCT	TS		4 yr
11	62	F	23	28	yes	5.4	435	no	TC/TS		
12	67	M	10	29	no	5.7	489	OCT	TS		
13	69	M	15	24	yes	15.4	585	OCT	TS		

Pt, Patients; DD, duration of disease; HY, hypertension; BMI, body mass index; PT, previous treatment; CAB, cabergoline; OCT, octreotide; NS, neurosurgery (TS, transsphenoidal; TC, transcranial); RT, replacement therapy (GS, gonadal steroids; C, cortisone acetate); RxT, radiotherapy.

[a] Time before starting treatment with SR-lanreotide.

velocities and the E wave deceleration time were calculated in three to five consecutive cardiac cycles, showing reliable velocity profiles.

Statistical analysis

Unless otherwise specified, all data are presented as mean ± SEM. Differences concerning hormonal values and echocardiographic parameters at different time points of the study were compared by the Wilcoxon rank-test. The Mann-Whitney test was used for comparing patients, controls, and subgroups of patients. $P < 0.05$ was considered significant. Statistical analysis was made using a Statview 4.02 software for McIntosh.

Results

Influence of SR-lanreotide on GH and IGF-I plasma levels

Mean pretreatment GH and IGF-I values were 10.1 ± 2.2 ng/mL and 511.0 ± 33.0 ng/mL, respectively. The evolution of GH/IGF-I levels throughout the study period is shown in Fig. 1. At the end of the study, mean plasma GH and IGF-I levels were 3.9 ± 0.9 ng/mL ($P < 0.005$ *vs.* baseline; 7 of 13 patients with GH < 2.5 ng/mL) and 305.8 ± 34.2 ng/mL ($P < 0.05$ *vs.* baseline, 8 of 13 patients with normal age-corrected IGF-I), respectively.

Pretreatment echo-Doppler parameters in acromegalics vs. controls

Data comparing acromegalic patients and controls are summarized in Tables 2 and 3. Acromegalic patients showed significantly higher LVM ($P < 0.0005$) and LVMI ($P < 0.0005$), meeting the criteria for LVH in 10 cases (2 males, 8 females), including 2 of the 3 hypertensive patients and 7 of the 9 patients previously treated with octreotide and/or cabergoline.

Acromegalics also displayed some differences concerning dynamic parameters, mostly indicative of impaired diastolic function (higher IRT, $P = 0.005$ *vs.* controls; lower baseline E/A ratio, $P < 0.05$ *vs.* controls) (25).

Short-term effects of SR-lanreotide on hemodynamic and echo-Doppler parameters

Blood pressure and heart rate were unchanged after a single injection of SR-lanreotide. A significant decrease in IVSDT, PWDT, and LVSV, together with a significant improvement of both LVM and LVMI ($P < 0.05$ for all parameters), was observed at T2. At the same time, a slight, but significant, decrease of both A wave and IRT were observed ($P < 0.05$ for both parameters), indicating a modest improvement of the left ventricular diastolic function, whereas systolic parameters were unchanged.

Evolution of hemodynamic and echo-Doppler parameters throughout the 12-month study period

Blood pressure and heart rate remained unchanged throughout the whole study period. Most echo-Doppler parameters continued to improve throughout the study period, although no more differences could be found between T4 and T5, indicating that the maximal cardiac effects were generally obtained after 6 months of treatment and sustained at 12 months. The decrease of both LVM and LVMI ($P < 0.005$ *vs.* baseline for both parameters at T3, T4, and T5) was accompanied by a significant reduction of IVSDT and PWDT, which were further decreased at T3 ($P < 0.05$ for both parameters), T4, and T5 ($P < 0.05$ and $P < 0.005$ at both time points, respectively). A significant reduction of left ventricular diastolic and systolic volumes (LVDV and LVSV) was also observed at T3 ($P < 0.05$ for both parameters), T4, and T5 ($P < 0.05$ and $P < 0.005$ at both time points, respectively). A significant decrease of both A-wave and IRT was observed at T3, T4, and T5 ($P < 0.05$ and $P < 0.005$ at each time point, respectively), indicating an improvement of the left ventricular diastolic function (*i.e.* the relaxation properties), which was also maximal at T4. In contrast, no significant reduction of left ventricular internal diameters was observed, with respect to pretreatment values.

Effects of SR-lanreotide on the LVM

Although LVM and LVMI were still higher in acromegalics than in controls at T5 ($P < 0.001$ for both parameters), 6 of 10 patients who met the criteria for LVH when they entered the study did not meet this criteria anymore at T5. Analysis of individual data revealed that, in this series, such a LVH reduction tended to be more frequent in younger patients, LVMI being normalized in 5 of 5 patients less than 45 yr old (100%) but in only 1 of 5 patients more than 45 yr old (20%). Accordingly, the mean age of patients who normalized LVMI was significantly lower that of patients who

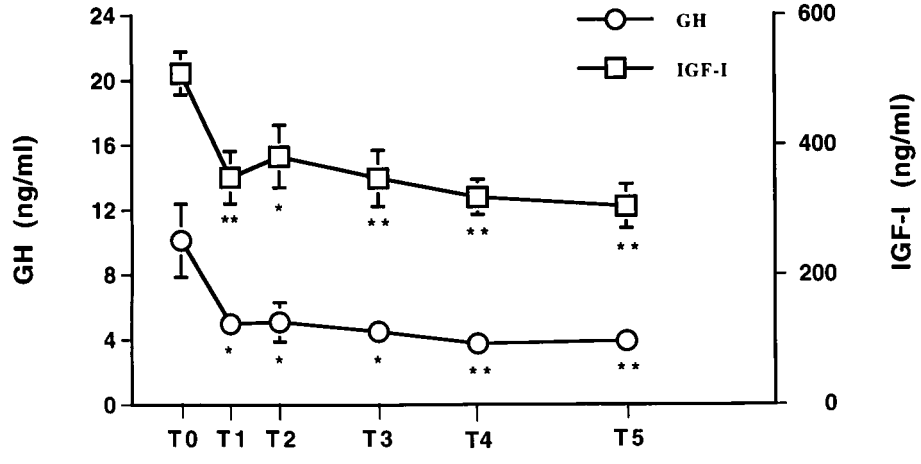

FIG. 1. GH (○) and IGF-I (□) plasma levels, before and during SR-lanreotide treatment (*, $P < 0.05$; **, $P < 0.005$ *vs.* baseline), in a series of 13 acromegalic patients with postoperative ongoing disease.

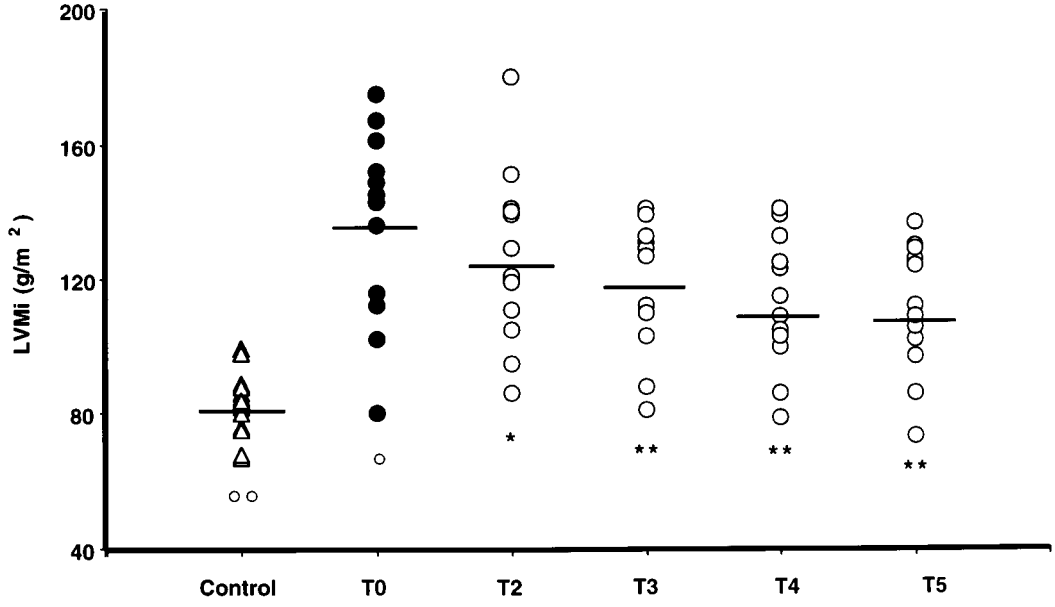

FIG. 2. LVMI values in control subjects (△) and in 13 acromegalic patients at baseline (●) and during SR-lanreotide treatment (○) (*, $P < 0.05$ *vs.* basal; **, $P < 0.005$ *vs.* basal; °, $P < 0.005$ *vs.* control; °°, $P < 0.005$ *vs.* acromegalic patients at all time points).

TABLE 2. Cardiac parameters (mean ± SEM) in controls (n = 13) and acromegalics (n = 13) before and during SR-lanreotide treatment

Cardiac parameters	Controls	Acromegalics				
		T0	T2	T3	T4	T5
Hemodynamic parameters						
Heart rate (beats/min) (HR)	72.3 ± 0.6	71.7 ± 1.4	73.1 ± 0.9	73.1 ± 0.9	72.3 ± 0.5	73.3 ± 0.4
Systolic arterial pressure (mmHg) (SAP)	120.3 ± 1.2	126.5 ± 5.2	125.0 ± 1.8	125.7 ± 1.6	124.3 ± 1.8	124.2 ± 1.6
Diastolic arterial pressure (mmHg) (DAP)	77.3 ± 0.9	82.3 ± 3.2	81.1 ± 1.4	81.1 ± 0.7	81.1 ± 1.1	80.0 ± 1.1
Morphological parameters						
Left ventricular end diastolic diameter (mm) (LVEDD)	47.5 ± 0.7	54.3 ± 1.7	53.2 ± 1.6	52.8 ± 1.6	52.6 ± 1.6	52.2 ± 1.6
LVESD (mm)	30.5 ± 1.0	35.8 ± 1.6	34.5 ± 1.5	33.6 ± 1.5	33.4 ± 1.5	33.5 ± 1.5
IVSDT (mm)	8.3 ± 0.3	10.2 ± 0.4[a]	9.9 ± 0.4[b]	9.5 ± 0.3[b]	9.1 ± 0.3[b]	9.1 ± 0.3[b]
Interventricular septum systolic thickness (mm) (IVSST)	15.7 ± 0.4	18.0 ± 1.0	18.8 ± 0.6	17.4 ± 0.5	18.7 ± 0.8	18.4 ± 0.8
PWDT (mm)	7.9 ± 0.2	10.0 ± 4.4[c]	9.5 ± 0.3[b]	9.0 ± 0.2[b]	8.8 ± 0.2[d]	8.8 ± 0.2[d]
PWST (mm)	14.8 ± 0.3	17.3 ± 0.5	17.0 ± 0.4	16.2 ± 0.4	15.6 ± 0.3	15.1 ± 0.4
LVM (g)	146.3 ± 7.7	263.5 ± 15.1[c]	241.1 ± 10.7[d]	230.3 ± 11.4[d]	214.9 ± 10.6[d]	211.8 ± 10.2[d]
LVMI (g/m^2)	82.8 ± 2.7	137.1 ± 7.5[c]	125.9 ± 6.9[b]	120.0 ± 5.4[d]	111.7 ± 5.7[d]	110.3 ± 5.2[d]
LVDV (ml)	107.7 ± 4.6	156.1 ± 14.4[a]	151.5 ± 14.0	141.3 ± 12.5[b]	142.6 ± 12.3[b]	141.9 ± 12.2[b]
LVSV (ml)	29.3 ± 2.1	48.8 ± 6.8[a]	44.9 ± 6.3[b]	42.4 ± 5.9[b]	40.1 ± 5.2[d]	39.6 ± 5.2[d]

[a] $P < 0.05$ *vs.* control.
[b] $P < 0.05$ *vs.* basal.
[c] $P < 0.005$ *vs.* control.
[d] $P < 0.005$ *vs.* basal.

did not (mean ± SD; 38.0 ± 16.2 *vs.* 58.2 ± 3.3 yr, $P < 0.05$). The estimated duration of the disease was also significantly shorter in patients who normalized LVMI than in those who did not (mean ± SD; 8.8 ± 3.9 *vs.* 17.9 ± 3.9 yr, $P < 0.02$). In contrast, no significant difference could be found concerning pretreatment echo-Doppler parameters between both groups (data not shown). Neither could any significant difference be found between plasma GH and IGF-I levels at T0 and T5 between these two groups (data not shown).

Discussion

The therapeutic goals in acromegaly are to normalize plasma GH/IGF-I levels and to prevent the long-term complications of the disease, to improve both life expectancy and the quality of life of these patients.

It has long been recognized that cardiovascular involvement greatly contributes to the increased morbidity and mortality observed in acromegalics. However, the concept that GH/IGF-I hypersecretion is able to induce, by itself, a specific cardiomyopathy, has emerged more recently, supported by both *in vivo* and *in vitro* observations (4, 28). In particular, receptors for both GH (29) and IGF-I (30) are expressed by myocardial cells, and there is evidence that IGF-I is able to increase the size of cultured cardiomyocytes (31). In addition, cardiac abnormalities can be found in young normotensive acromegalics with normal glucose tolerance, who should

TABLE 3. Cardiac parameters (mean ± SEM) in controls (n = 13) and acromegalics (n = 13) before and during SR-lanreotide treatment

Cardiac parameters	Controls	Acromegalics				
		T0	T2	T3	T4	T5
Systolic parameters						
Ejection fraction (EF%)	61.0 ± 2.1	68.6 ± 2.0	70.8 ± 2.2	70.2 ± 2.4	72.1 ± 1.9	71.9 ± 2.1
FS%	36.0 ± 1.7	34.1 ± 1.9	34.8 ± 2.0	36.3 ± 2.0	36.4 ± 1.9	36.1 ± 2.0
SV (ml)	79.9 ± 3.3	107.1 ± 1.3[a]	106.6 ± 9.4	98.8 ± 8.9	102.5 ± 8.8	101.6 ± 8.9
CO (l/min)	5.8 ± 0.2	7.5 ± 0.7	7.7 ± 0.6	7.1 ± 0.6	7.3 ± 0.6	7.2 ± 0.6
ESS (dynes/cm^2)	56.2 ± 3.5	60.5 ± 6.3	57.5 ± 3.1	59.1 ± 3.7	57.8 ± 3.4	61.2 ± 3.9
MVCFc (circ/sec)	1.0 ± 0.03	1.4 ± 0.1[a]	1.4 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	1.5 ± 0.1
Diastolic parameters						
E (cm/sec)	70.0 ± 2.0	67.5 ± 3.0	62.6 ± 3.4	63.8 ± 3.6	65.2 ± 3.9	65.2 ± 3.9
A (cm/sec)	39.0 ± 2.8	51.0 ± 3.0[a]	49.0 ± 3.3[b]	44.8 ± 2.2[b]	45.2 ± 2.2[b]	45.2 ± 2.1[b]
Ratio (E/A)	2.0 ± 0.1	1.3 ± 0.1[c]	1.2 ± 0.1	1.4 ± 0.1	1.3 ± 0.1	1.4 ± 0.1
IRT (m/sec)	89.3 ± 1.6	109.1 ± 4.6[c]	98.7 ± 3.6[b]	91.9 ± 2.8[d]	92.3 ± 3.2[d]	92.2 ± 3.0[d]
E wave deceleration time (m/sec) (DTE)	187.0 ± 3.3	214.6 ± 7.6[a]	210.3 ± 5.7	210.0 ± 6.0	208.5 ± 8.9	206.4 ± 8.3

[a] $P < 0.05$ *vs.* control.
[b] $P < 0.05$ *vs.* basal.
[c] $P < 0.005$ *vs.* control.
[d] $P < 0.005$ *vs.* basal.

represent a good human model for the study of precocious myocardial alterations almost caused by GH/IGF-I hypersecretion (25). During the past 15 yr, several reports on echo-Doppler and isotopic studies in acromegalics have been published, and a model of the natural history of acromegalic heart disease has been proposed by Saccà *et al.* (4). According to such a model, the early stage of the disease is characterized by functional abnormalities consisting of an hyperkinetic syndrome with an increased contractility and a high cardiac CO, followed by an intermediate stage characterized by a concentric biventricular myocardial hypertrophy associated with diastolic dysfunction at rest and systolic dysfunction on effort. Impaired cardiac performance is rare and appears only at the end stage of the disease. In the present series, the main echo-Doppler abnormalities observed before medical consisted of an increased LVMI associated with an impaired diastolic function, suggesting that most patients had an intermediate-staged cardiomyopathy. None had evidence of systolic dysfunction at rest. The baseline significant increase of SV and MVCFc observed in acromegalics, when compared with controls, could be a residual part of the hyperkinetic syndrome (32). In addition, the baseline-increased LVM could reflect the volume overload caused by the sodium and water retention induced by GH/IGF-I hypersecretion (33) and to the action of the renin-angiotensin system (4).

An important issue is to determine the reversibility of cardiac abnormalities, along with GH/IGF-I reduction or normalization. There is now accumulating evidence that myocardial hypertrophy can be rapidly improved by octreotide: a significant reduction in LVM, IVSDT, and PWDT can be observed after a short-term octreotide treatment, in acromegalics with LVH (14); and this improvement is sustained at 6 months (13, 16) and 12 months (28) of treatment. Improvement of subclinical diastolic dysfunction has also been reported after 6 months of octreotide treatment (15, 16), a finding in agreement with the correlation found between LVH and diastolic dysfunction in these patients (34). In contrast, the effect of GH/IGF-I normalization on systolic performance when impaired is still controversial and may occur later (28, 35); it is difficult to decide to what extent the rapid hemodynamic improvement, observed after octreotide treatment in acromegalics with end-stage disease (36), reflects a specific improvement in the acromegalic cardiomyopathy or a significant reduction in volume overload. To our knowledge, this is the first study reporting the effects of an SR formulation of a SRIF analog, SR-lanreotide, on LVMI and diastolic relaxation properties in acromegaly. SR formulations have the advantage of avoiding the fluctuations in GH concentrations that may occur throughout the day with conventional octreotide treatment and allowing a better compliance to the treatment. A good indication is represented by patients with ongoing disease after surgery, in whom long-term control of the disease should be achieved by medical treatment, radiotherapy, or both.

It is interesting to note that some improvement in ventricular mass and left ventricular relaxation properties could be observed after a single injection of SR-lanreotide. This improvement was reinforced after 3 months of the same drug dose, whereas the subsequent improvement observed between the 3rd and 6th months of treatment is likely to reflect the increase of the SR-lanreotide dose in a large subset of patients. Thereafter, the improvement of LVMI and diastolic relaxation properties was sustained until the 12th month of treatment, whereas systolic parameters remained grossly unchanged throughout the study. These findings are in agreement with previous data reported in octreotide-treated patients (16).

A significant subset of patients with LVH before treatment did not continue to meet the criteria for LVH after SR-lanreotide treatment (6/10). Because LVH is arbitrarily defined by LVMI exceeding a conventional cut-off value, this does not mean that all these patients had their LVM really normalized. In fact, the mean LVM and LVMI were still significantly above control values at the end of the treatment period. However, a significant reduction of LVMI can be used as a criteria for the identification of patients with a reversible acromegalic cardiomyopathy. Interestingly, all but one of these patients were less than 45 yr old, a finding that is likely to reflect the fact that young patients usually

have a shorter exposure to GH/IGF-I hypersecretion (25) and a lower incidence of hypertension (37).

We conclude that SR-lanreotide is able to induce a significant improvement of LVMI and diastolic function in acromegalic patients with postsurgical persisting disease. Determining whether such beneficial effects will improve the life expectancy of these patients should deserve further long-term studies.

Acknowledgments

The authors are grateful to Ms. Antonella Balestrini, Gioacchino Romano, and Ercole Mazzei for their excellent technical assistance.

References

1. **Kahaly G, Stover C, Beyer J, Mohr-Kahaly S.** 1992 Relation of endocrine and cardiac findings in acromegalics. J Endocrinol Invest. 15:13–18.
2. **Lopez-Velasco R, Escobar-Morreale HF, Vega B, et al.** 1997 Cardiac involvement in acromegaly: specific cardiomyopathy or consequence of systemic hypertension? J Clin Endocrinol Metab. 82:1047–1053.
3. **Colao A, Merola B, Ferone D, Lombardi G.** 1997 Acromegaly. J Clin Endocrinol Metab. 82:2777–2781.
4. **Saccà L, Cittadini A, Fazio S.** 1994 Growth hormone and the heart. Endocr Rev. 15:555–572.
5. **Fazio S, Cittadini A, Sabatini D, Merola B, Colao AM, Biondi B.** 1993 Evidence for biventricular involvement in acromegaly: a Doppler echocardiographic study. Eur Heart J. 14:26–33.
6. **Just H, Nieschlag E, Nicolescu RF, Kroger FJ, Overzier C.** 1994 Cardiac function in acromegaly. A clinical and hemodynamic study. Acta Cardiol. 29:89–103.
7. **Hayward RP, Emanuel RW, Nabarro JDN.** 1987 Acromegalic heart disease: influence of treatment of the acromegaly on the heart. Q J Med. 237:41–58.
8. **Lieberman SA, Hoffman AR.** 1990 Sequelae to acromegaly: reversibility with treatment of the primary disease. Horm Metab Res. 22:313–318.
9. **Lie JT, Grossman SJ.** 1980 Pathology of the heart in acromegaly: anatomic findings in 27 autopsied patients. Am Heart J. 100:41–52.
10. **Nabarro JDN.** 1987 Acromegaly. Clin Endocrinol (Oxf) 26:481–512.
11. **Hradec J, Marek J, Petrasek J.** 1988 The nature of cardiac hypertrophy in acromegaly: an echocardiographic study. Cor Vasa. 30:186–199.
12. **Hradec J, Marek J, Kral J, Janota T, Poloniecki J, Malik M.** 1993 Long-term echocardiographic follow-up of acromegalic heart disease. Am J Cardiol. 72:205–210.
13. **Thuesen L, Christensen SE, Weeke G, Orskov H, Henningsen P.** 1989 The cardiovascular effects of octreotide treatment in acromegaly: an echocardiographic study. Clin Endocrinol (Oxf) 30:619–625.
14. **Lim MJ, Barkan AL, Buda AJ.** 1992 Rapid reduction of left ventricular hypertrophy in acromegaly after suppression of growth hormone hypersecretion. Ann Intern Med. 117:719–726.
15. **Pereira JL, Rodriguez-Puras MJ, Leal-Cerro A, et al.** 1991 Acromegalic cardiopathy improves after treatment with increasing doses of octreotide. J Endocrinol Invest. 14:17–23.
16. **Merola B, Cittadini A, Colao AM, et al.** 1993 Chronic treatment with the somatostatin analog octreotide improves cardiac abnormalities in acromegaly. J Clin Endocrinol Metab. 77:790–793.
17. **Gunal AI, Isik A, Celiker H, et al.** 1996 Short-term reduction of left ventricular mass in primary hypertrophic cardiomyopathy by octreotide injections. Heart. 76:418–421.
18. **Heron I, Thomas F, Dero M, Gancel A, Ruiz J M, Schatz B.** 1993 Pharmacokinetics and efficacy of a long-acting formulation of the new somatostatin analog BIM 23014 in patients with acromegaly. J Clin Endocrinol Metab. 76:721–727.
19. **Giusti M, Gussoni G, Cuttica CM, Giordano G, and the Italian Multicenter Slow Release Lanreotide Study Group.** 1996 Effectiveness and tolerability of slow release lanreotide treatment in active acromegaly: six-month report on an Italian multicenter study. J Clin Endocrinol Metab. 81:2089–2097.
20. **Al-Maskari M, Gebbie J, Kendall-Taylor P.** 1996 The effect of a new slow-release, long-acting somatostatin analogue, lanreotide, in acromegaly. Clin Endocrinol (Oxf) 45:415–421.
21. **Johnson MR, Chowdrey HS, Thomas F, Grint C, Lightman SL.** 1994 Pharmacokinetics and efficacy of the long-acting somatostatin analogue somatuline in acromegaly. Eur J Endocrinol. 130:229–234.
22. **Morange I, De Boisvilliers F, Chanson P, et al.** 1994 Slow release lanreotide treatment in acromegalic patients previously normalized by octreotide. J Clin Endocrinol Metab. 79:145–151.
23. **World Health Organization/International Society of Hypertension.** 1993 Guidelines for the management of mild hypertension: memorandum from WHO/ISH meeting. J Hypertens. 22:392–403.
24. **Sahn DJ, De Maria A, Kissio J, Weyman A.** 1978 The committee on M-mode standardization of the American Society of Echocardiography. Recommendations regarding quantification in M-mode echocardiography: results of a survey of echocardiography measurements. Circulation. 58:1072–1083.
25. **Minniti G, Jaffrain-Rea ML, Moroni C, et al.** 1998 Echocardiographic evidence for a direct effect of GH/IGF-I hypersecretion on cardiac mass and function in young acromegalics. Clin Endocrinol (Oxf) 49:101–106.
26. **Reicheck N, Wilson J, St John-Sutton M, Plappert TA, Goldberg S, Hirshfeld JW.** 1982 Non-invasive determination of left ventricular end-systolic stress: validation of the method and initial application. Circulation. 65:99–108.
27. **Devereux RB.** 1987 Detection of left ventricular hypertrophy by M-mode echocardiography. Anatomic validation, standardization and comparison to the other methods. Hypertension. [Suppl 2] 9:19–26.
28. **Lombardi G, Colao A, Ferone D, et al.** 1996 Cardiovascular aspects in acromegaly: effects of treatment. Metabolism. [Suppl 1] 45:57–60.
29. **Mathews LS, Enberg B, Norstedt G.** 1989 Regulation of rat growth hormone receptor gene expression. J Biol Chem. 17:9905–9910.
30. **Guse AH, Kiess W, Funk B, Kessler U, Berg I, Gercken G.** 1992 Identification and characterization of insulin-like growth factor receptors on adult rat cardiac myocytes: linkage to inositol 1, 4, 5-triphosphate formation. Endocrinology. 130:145–151.
31. **Ito H, Hiroe M, Hirata Y, Tsujino M, Adachi S, Shichiri M.** 1993 Insulin-like growth factor-I induced hypertrophy with enhanced expression of muscle specific genes in cultured rat cardiomyocytes. Circulation. 87:1715–1721.
32. **Thuesen L, Christensen SE, Weeke J, Orskow H, Henningsen P.** 1988 A hyperkinetic heart in uncomplicated acromegaly. Explanation of hypertension in acromegalic patients? Acta Med Scand. 223:337–343.
33. **McNight JA, McCance DR, Hadden DR, et al.** 1989 Basal and saline-stimulated levels of plasma atrial natriuretic factor in acromegaly. Clin Endocrinol (Oxf) 31:431–438.
34. **Cuocolo A, Nicolai E, Fazio S, Pace L, Maurea S, Cittadini A.** 1995 Impaired left ventricular diastolic filling in patients with acromegaly: assessment with radionuclide angiography. J Nucl Med. 36:196–201.
35. **Padayatty SJ, Perrins EJ, Belchetz PE.** 1996 Octreotide treatment increases exercise capacity in patients with acromegaly. Eur J Endocrinol. 134:554–559.
36. **Chanson P, Timsit J, Masquet C, et al.** 1990 Cardiovascular effects of the somatostatin analog octreotide in acromegaly. Ann Intern Med. 113:921–925.
37. **Minniti G, Moroni C, Jaffrain-Rea ML, et al.** 1998 Prevalence of hypertension in acromegalic patients: clinical measurement *vs.* 24-hour ambulatory blood pressure monitoring. Clin Endocrinol (Oxf) 48:149–152.