Clinical Endocrinology (2002) **56**, 65–71

Long-term effects of lanreotide SR and octreotide LAR® on tumour shrinkage and GH hypersecretion in patients

Giovanni Amato*, Gherardo Mazziotti*, Mario Rotondi*, Sergio Iorio*, Mauro Doga‡, Francesca Sorvillo*, Giovanni Manganella*, Francesco Di Salle†, Andrea Giustina‡ and Carlo Carella*

**Endocrinology Institute Second University of Naples,*
†Radiology Institute, University 'Federico II', Naples,
‡Department of Internal Medicine/Endocrine Section, University of Brescia, Brescia, Italy

(Received 8 March 2001; returned for revision 15 May 2001; finally revised 2 June 2001; accepted 27 September 2001)

Summary

BACKGROUND AND OBJECTIVE The therapeutic efficacy of lanreotide SR and octreotide LAR® has been studied widely in patients treated previously with neurosurgery and/or radiotherapy. These therapies limit the evaluation of the long-term effects of somatostatin analogues on tumour shrinkage. Neurosurgical and radiotherapy treatments cause irreversible anatomical changes in pituitary morphology, which can make accurate evaluation of tumour shrinkage difficult. The aim of this study was to investigate the therapeutic efficacy of lanreotide SR and octreotide LAR® in previously untreated patients with acromegaly. We aimed to investigate the long-term effects of these drugs on tumour shrinkage and growth hormone (GH) hypersecretion without the confounding influences of previous therapy.

PATIENTS AND METHODS Twenty-three newly diagnosed patients with acromegaly (14 women, nine men) with active disease began the study; of these, three were lost for follow-up, leaving a total of 20 patients to complete the study. Patients were assigned randomly to lanreotide SR (12 patients) and octreotide LAR® (eight patients), and the randomization stratified patients to assure a balance between the groups with respect to baseline tumour dimension, age and sex. Tumour volume was evaluated by magnetic resonance imaging of the sella, and calculated with the rotating ellipsoid formula. A morphological and biochemical evaluation was performed at baseline, 12 and 24 months after beginning lanreotide SR and octreotide LAR® treatment. A reduction of tumour volume of at least 10% was considered significant.

RESULTS Biochemical control increased progressively throughout the study in patients with microadenomas more than in patients with macroadenomas (70% *vs.* 10%; $P < 0{\cdot}05$) and without a difference between lanreotide SR and octreotide LAR® (41·0% *vs.* 37·5%; *P* not significant). After 12 months of treatment, mean tumour shrinkage was 28·3 ± 18·0%. A greater reduction was observed in macro- *vs.* microadenomas (40·5 ± 17·0% *vs.* 16·1 ± 8·0%, respectively; $P < 0{\cdot}05$). No statistical difference in the tumour shrinking effects of lanreotide SR *vs.* octreotide LAR® was observed (26·5 ± 17·3% *vs.* 31·1 ± 16·1%, respectively). At the 24th month of therapy, no further overall shrinkage was observed, compared to the 12-month evaluation (31·9 ± 17·2% *vs.* 28·3 ± 18·0%) at which there was no difference between lanreotide SR and octreotide LAR® (30·0 ± 17·2% *vs.* 34·8 ± 16·5%, respectively).

CONCLUSIONS This study showed that the new long-acting somatostatin analogues, lanreotide SR and octreotide LAR®, cause significant shrinkage of pituitary GH-secreting adenomas in previously untreated patients with acromegaly. This effect was more marked in macroadenomas than microadenomas, and did not correlate with control of GH hypersecretion.

In acromegaly, the therapeutic goal is to restore normal growth hormone (GH) secretory dynamics, normalize serum insulin-like growth factor-I (IGF-I) levels and shrink the pituitary mass (Giustina *et al*., 2000). Transsphenoidal adenomectomy is considered the most cost-effective and rapid initial treatment for acromegalic patients, with a success rate ranging between 48 and 91% (Melmed *et al.*, 1998; Freda & Wardlaw, 1999).

Medical therapy has assumed a more prominent role in the treatment of acromegaly as the number and efficacy of available therapies have increased (Melmed *et al.*, 1998). Octreotide, administered subcutaneously (s.c.) three times daily, has been used in the treatment of acromegaly for more than 10 years (Plewe *et al.*, 1984; Ezzat *et al.*, 1992; Giustina *et al.*, 1996). Recently, true slow release somatostatin analogues (SMS-a), such as lanreotide SR, 30 or 60 mg, which can be administered

Correspondence: Carlo Carella PhD, Via Crispi 44, 80121 Naples, Italy. Tel/Fax: +39-81-566-6632; E-mail: carlo.carella@unina2.it

intramuscularly (i.m.) every 7–14 days or octreotide LAR®, 10–30 mg, given i.m. every 28 days, have been developed (Marek *et al.*, 1994; Morange *et al.*, 1994; Stewart *et al.*, 1995; Giusti *et al.*, 1996; Lancranjan *et al.*, 1996; Caron *et al.*, 1997; Flogstad *et al.*, 1997; Gillis *et al.*, 1997; Davies *et al.*, 1998). These drugs improve compliance and exhibit similar effects on the control of disease as standard s.c. octreotide therapy.

Recently, the effects of long-acting drugs on GH hypersecretion have been compared and a slightly better effect of octreotide LAR® *vs.* lanreotide SR in the biochemical control of acromegaly has been demonstrated (Cozzi *et al.*, 1999; Turner *et al.*, 1999; Chanson *et al*., 2000). However, in these studies, previous therapies have limited the evaluation of the long-term therapeutic efficacy of SMS-a on tumour shrinkage. In fact, previous neurosurgical and radiotherapy treatments cause irreversible anatomical changes of pituitary morphology, which can make accurate evaluation of tumour shrinkage difficult (Barkan *et al.*, 1988).

The aim of this study was to investigate the therapeutic efficacy of lanreotide SR and octreotide LAR® in previously untreated patients with acromegaly. We aimed to investigate the long-term effect of these drugs on tumour shrinkage and GH hypersecretion without the confounding influences of previous therapy.

Patients and methods

Twenty-three newly diagnosed patients with acromegaly (14 women, nine men) with active disease entered the study (Table 1). Their mean age was 55·0 years (range 40–72). In all cases the diagnosis was established based on clinical, laboratory and neuroimaging data (Duncan & Wass, 1999). Thirteen patients in the study group refused neurosurgery, while 10 were of high anaesthetic risk due to various systemic diseases (four patients with cardiac failure, four with chronic obstructive respiratory disease and two with severe allergy), and therefore received long-acting SMS-a (lanreotide SR and octreotide LAR®) treatment as first-line therapy. Patients were randomly assigned to the two drugs. The computerized randomization stratified patients to assure balance between the groups with respect to tumour volume at baseline (micro- and macroadenomas), age and sex. The study was approved by our Local Ethical Committee, and all patients gave written informed consent.

Twelve patients received an i.m. injection of lanreotide SR 30 mg (Ipstyl®, Ipsen Biotech Laboratory, Milan, Italy) sequentially every 10 days (Table 1). On the basis of the clinical and biochemical responses to treatment (target basal GH level, 5 mU/l), a reduction in the time interval between injections (from 10 to 7 days) was actioned after 3 months. As a result of these dose-adjustments, five patients remained on 10-day administration and seven were transfered to a 7-day administration schedule. Eleven patients underwent therapy with octreotide LAR® (Sandostatin® LAR®, Novartis Pharma, Basel, Switzerland) at an initial dosage of 20 mg every 28 days (Table 1). On the basis of the clinical and biochemical response to treatment (evaluated as above), the dose was modified (after three administrations) to 30 mg (five patients)

Table 1 Baseline clinical and demographic data of the study population

Patient no.	Age	Sex	Tumoural mass	Adenoma volume (ml)	GH (mU/l)	IGF-I (ng/ml)	Drugs	Therapeutic regimen
1	40	M	Macroadenoma	0·8	76	456·7	LSR	30 mg/7 days
2	40	M	Macroadenoma	0·8	70	456·7	OLR	30 mg/28 days
3	59	M	Macroadenoma	0·9	72	542·2	OLR	30 mg/28 days
4	56	F	Macroadenoma	0·9	112	649·5	LSR	30 mg/7 days
5	56	F	Macroadenoma	0·9	114	649·5	LSR	30 mg/7 days
6	44	F	Macroadenoma	1·9	70	568·5	LSR	30 mg/7 days
7	47	F	Macroadenoma	1·4	66	855·0	OLR	30 mg/28 days
8	59	F	Macroadenoma	0·6	40	399·7	LSR	30 mg/7 days
9	68	F	Macroadenoma	0·8	36	780·0	OLR	30 mg/28 days
10	72	M	Macroadenoma	0·9	80	490·0	LSR	30 mg/10 days
11	66	F	Microadenoma	0·3	30	380·0	LSR	30 mg/7 days
12	60	M	Microadenoma	0·3	20	720·0	LSR	30 mg/10 days
13	45	F	Microadenoma	0·3	52	600·0	LSR	30 mg/7 days
14	40	F	Microadenoma	0·2	100	349·5	OLR	20 mg/28 days
15	41	F	Microadenoma	0·2	26	348·0	OLR	20 mg/28 days
16	40	M	Microadenoma	0·3	38	895·5	LSR	30 mg/10 days
17	50	F	Microadenoma	0·2	181	499·5	LSR	30 mg/10 days
18	61	M	Microadenoma	0·2	30	411·7	OLR	10 mg/28 days
19	62	F	Microadenoma	0·2	16	919·5	OLR	20 mg/28 days
20	59	M	Microadenoma	0·5	72	360·0	LSR	30 mg/10 days

LSR, lanreotide SR; OLR, octreotide LAR®.

or 10 mg (one patient) every 28 days. Three patients receiving octreotide LAR® were lost to follow-up (one chose neurosurgery after the start of medical therapy, two were lost to hospital control), leaving eight patients for the clinical evaluation (Table 1).

Visual field examination was performed using Goldman perimetry at baseline and after 12 and 24 months of treatment.

Magnetic resonance imaging (MRI) of the sella, using 0·5 T M_t unit (Vectra, General Electric, Milan, Italy), after intravenous (i.v.) administration of gadolinium was performed at baseline and after 12 and 24 months of SMS-a therapy. The tumour size was evaluated in three dimensions: maximal vertical (V) diameter was measured on the coronal images, and maximal anteroposterior (AP) and transverse (T) diameters on the axial images. The volume of the tumour was calculated as the volume of a rotating ellipsoid, with the following formula: $\pi/6$ (V × AP × T) (Di Chiro & Nelson, 1962). All patients had a pituitary adenoma. On MRI, in particular, a microadenoma (maximal diameter ≤ l0 mm) was observed in 10 patients, and a macroadenoma (maximal diameter > 10 mm) in the other 10 patients (Table 1). Sixty per cent of patients with a macroadenoma had a maximal diameter above 20 mm and in none was it greater than 35 mm. For the objective assessment, selected hard copy images of pituitary region were digitized. Pretreatment and post-treatment scans were evaluated by two radiologists in joint consultations. The observers were blinded to the dates of the scans. A reduction in tumour volume of at least 10% was considered significant shrinkage (Newman *et al.*, 1998). Moreover, the degree of shrinkage was subgrouped into three categories: 10–25% mass reduction, 25–50% and more than 50% shrinkage (Newman *et al.*, 1998). For the purpose of this study, biochemical evaluation of patients was assessed at baseline (T0), 12 (T12) and 24 (T24) months after the starting of lanreotide SR and octreotide LAR® treatment. GH values were evaluated as the mean of 8-hourly samplings between 08·00 and 15·00 h. Serum GH was measured by an immunoradiometric assay (Dia Sorin, Saluggia, Italy). The assay sensitivity was 0·2 mU/l, the intra-assay and interassay coefficients of variation were 2·1% and 4%, respectively. IGF-I was measured in fasting blood samples at 08·00 h by immunoradiometric assay (DSL, Webster, TX, USA). The sensitivity of the assay was 0·8 mg/ml. The intra-assay coefficients of variation were 3·4%, 3·0% and 1·5% for low, medium and high points of the standard curve, respectively. The interassay coefficients of variation were 8·2%, 1·5% and 3·7% for low, medium and high points of the standard curve, respectively. The biochemical aimsof treatment were to obtain serum IGF-I levels in the normal range for sex and age and a mean of the 8-h GH profile (hourly sampling) less than 5 mU/l (Orme *et al.*, 1998).

Statistical analysis

Statistical analysis was performed using the SPSS statistical package. Paired and un-paired data and percentages were compared by *t*-test and chi-square test, with Fisher's correction, when appropriate. All results are expressed as mean ± SD. A value of $P < 0{\cdot}05$ was considered significant for all tests.

Results

At study entry, the mean pituitary adenoma volume for all patients was 0·63 ± 0·47 ml (range 0·18–1·98). Ten patients had a microadenoma with a mean volume of 0·26 ± 0·09 ml (range 0·18–0·50), while the other 10 had a macroadenoma with a mean volume of 1·00 ± 0·40 ml (range 0·61–1·98). While basal GH values were higher in patients with macroadenomas than microadenomas, no statistical difference in serum IGF1 levels was observed between the two groups (Table 2). Moreover, at baseline, no statistical differences were observed between patients treated with lanreotide SR and octreotide LAR® for the same parameters (Table 3).

Only three patients (cases 4, 6 and 7) had modest visual field abnormalities (quadrantanopia) at baseline.

After 12 months of SMS-a therapy, the mean tumour volume in all patients was 0·42 ± 0·30 ml (range 0·16–1·1), with a mean reduction of 28·3 ± 18·0% (range 4·0–62·5%) with respect to

Table 2 Biochemical and morphological data in patients with macro- and microadenomas: basal and therapeutic responses

	Macroadenoma	Microadenoma	*P*-value
Basal serum GH levels (μg/l)	73·6 ± 25·0	40·2 ± 27·0	< 0·05
Basal IGF-I levels (ng/ml)	584·0 ± 148·0	548·4 ± 225·0	NS
Patients attaining GH values < 5·0 mU/l at T12 (%)	10·0	60·0	< 0·05
Patients attaining GH values < 5·0 mU/l at T24 (%)	10·0	90·0	< 0·05
Patients attaining normal IGF-I-values at T12 (%)	20·0	70·0	NS
Patients attaining normal IGF-I-values at T24 (%)	40·0	70·0	NS
Shrinkage (% volume reduction) at T12	40·5 ± 17·0	16·1 ± 8·0	< 0·05
Shrinkage (% volume reduction) at T24	43·7 ± 16·8	20·2 ± 10	< 0·05

T12, 12th month of therapy; T24, 24th month of therapy. The data are expressed as mean ± SD. NS, not significant.

Table 3 Biochemical and morphological data in acromegalic patients undergoing treatment with lanreotide SR and octreotide LAR®

	Lanreotide SR	Octreotide LAR®	*P*-value
Macroadenomas/microadenomas	6/6	4/4	NS
Basal serum GH levels (mU/l)	60·2 ± 30·6	52·0 ± 31·4	NS
Basal IGF-I levels (ng/ml)	565·7 ± 198·7	567·8 ± 179·0	NS
Patients attaining GH values < 5·0 mU/l at T12 (%)	33·3	37·5	NS
Patients attaining GH values < 5·0 mU/l at T24 (%)	58·3	50·0	NS
Patients attaining normal IGF-I-values at T12 (%)	50·0	37·5	NS
Patients attaining normal IGF-I-values at T24 (%)	66·7	50·0	NS
Shrinkage (% volume reduction) at T12	26·5 ± 17·3	31·1 ± 16·1	NS
Shrinkage (% volume reduction) at T24	30·0 ± 17·2	34·8 ± 16·5	NS

T12, 12th month of therapy; T24, 24th month of therapy. The data are expressed as mean ± SD. NS, not significant.

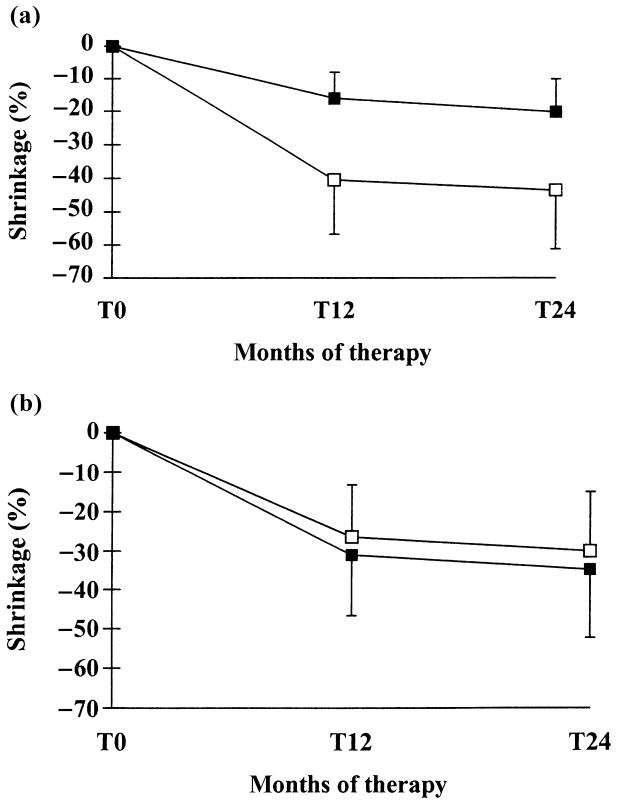

Fig. 1 (a) Shrinkage rates in acromegalic patient with micro- (■) and macroadenomas (□). (b) Shrinkage rates in acromegalic patients during treatment with lanreotide SR (□) and octreotide LAR® (■).The data are expressed as mean ± SD. $P < 0{\cdot}05$. T0: before therapy; T12: 12 th month of therapy; T24: 24th month of therapy.

basal values. The adenoma shrinkage was 10–25% in 10 cases (six treated with lanreotide SR, four treated with octreotide LAR®), 25–50% in seven cases (four treated with lanreotide SR, three treated with octreotide LAR®) and > 50% in two cases (one treated with lanreotide SR, one treated with octreotide LAR®). In only one patient (case 20) was no shrinkage was observed. Tumour shrinkage was greater in macro- than in microadenomas (40·5 ± 17·0% *vs.* 16·1 ± 8·0%, respectively; $P < 0{\cdot}05$; Fig. 1a). In particular, in all patients with microadenomas, the shrinkage was less than 25%, whereas it was greater than 25% in 9/10 patients with macroadenomas ($P < 0{\cdot}05$; e.g. case 9, Fig. 2). No statistical difference in tumour shrinkage was observed between lanreotide SR and octreotide LAR® (26·5 ± 17·3% *vs.* 31·1 ± 16·1%, respectively; Fig. 1b).

A slight improvement in visual fields was found in all three of the patients who had abnormal findings.

After 12 months of therapy, GH levels below 5 mU/l were observed in 6/10 patients with a microadenoma and in only one patient with a macroadenoma ($P < 0{\cdot}05$; Table 2). IGF-I-values were normalized in 7/10 patients with a microadenoma and in 2/10 patients with a macroadenoma (*P* not significant; Table 2). No statistical difference was observed between the two drugs in attaining target GH and IGF-I levels (Table 3).

After 24 months of therapy the mean tumour volume in all patients was 0·39 ± 0·25 ml (range 0·14–1·00), with no significant further shrinkage when compared to the 12-month evaluations (31·9 ± 17·2% *vs.* 28·3 ± 18·0%; *P* not significant; Figs 1a,b and 2) and with no difference between lanreotide SR and octreotide LAR® (30·0 ± 17·2% *vs.* 34·8 ± 16·5%, respectively; *P* not significant; Table 3). The percentage of patients with 'safe' GH values and a normal serum IGF-I level for sex and age increased from 30% (one patient with a macroadenoma, five patients with microadenomas) to 40% (one patient with a macroadenoma, seven patients with microadenomas), with no difference between lanreotide SR and octreotide LAR® (33·3% *vs.* 25·0% at T12 and 41·0% *vs.* 37·5% at T24).

Discussion

This study, performed in previously untreated patients with acromegaly, showed that long-acting SMS-a induces significant shrinkage in most patients, particularly those with GH-secreting macroadenomas. This effect was not correlated with the control

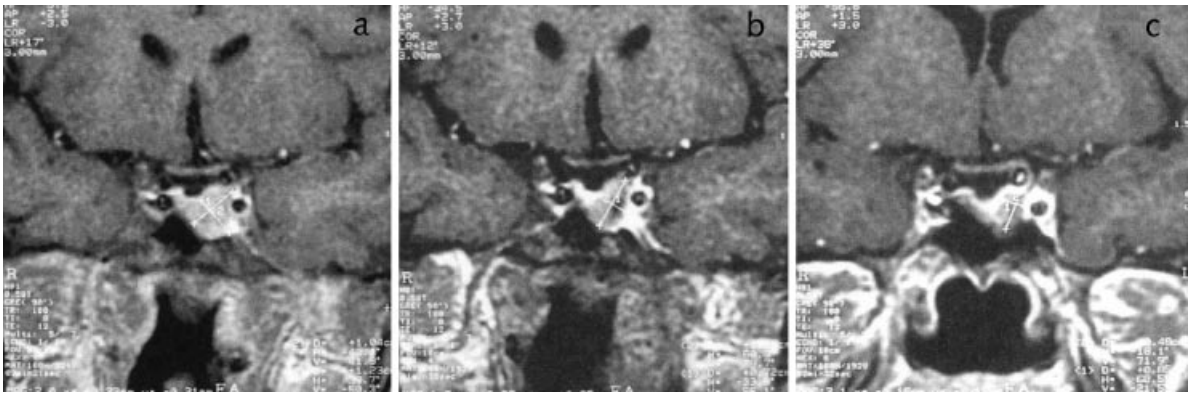

Fig. 2 Tumour shrinkage during depot SMS-a therapy. Coronal plane, gadolinium-enhanced T1-weighted MRI scans of a macroadenoma (case 9) at the same level through the pituitary fossa before (a) and after 12 (b) and 24 (c) months of lanreotide SR therapy.

of GH hypersecretion which is more evident in patients with microadenomas.

Transsphenoidal surgery is generally accepted as the initial therapy for most patients with acromegaly (Freda & Wardlaw, 1999). In this context, medical therapy has been used as an adjunctive treatment, although the progressive development of new compounds and easier administration schemes have encouraged first-line medical therapy (Ferone *et al*., 2000). Since most reports have studied the effects of SMS-a in previously treated patients with acromegaly, the estimation of the real efficacy of these drugs on tumour shrinkage has been difficult (Plewe *et al.*, 1984; Ezzat *et al.*, 1992; Marek *et al.*, 1994; Morange *et al.*, 1994; Stewart *et al.*, 1995; Giusti *et al.*, 1996; Giustina *et al.*, 1996; Lancranjan *et al.*, 1996; Caron *et al.*, 1997; Flogstad *et al.*, 1997; Gillis *et al.*, 1997; Davies *et al.*, 1998; Cozzi *et al.*, 1999; Turner *et al.*, 1999). In our study, the use of long-acting SMS-a as the sole treatment tool allowed us to make an accurate estimation of the long-term hormonal and morphological effects of these drugs.

In the literature, data concerning the effects of lanreotide SR and octreotide LAR® on tumour shrinkage are scarce, nonhomogeneous and difficult to evaluate (Marek *et al.*, 1994; Morange *et al.*, 1994; Stewart *et al.*, 1995; Giusti *et al.*, 1996; Lancranjan *et al.*, 1996; Caron *et al.*, 1997; Flogstad *et al.*, 1997; Gillis *et al.*, 1997; Davies *et al.*, 1998). In fact, transsphenoidal resection induces anatomical alterations of the pituitary sella, which could subsequently be modified over subsequent months or years, causing poor reproducibility of imaging evaluation (Naidich & Russel, 1999). On the other hand, packing materials placed into the sella may re-absorb and the volume of the residual mass may decrease, mimicking a shrinkage effect (Naidich & Russel, 1999). Radiotherapy also modifies pituitary imaging: in fact, it causes fibreotic changes in the sellar contents, which do not allow a precise tracing of the tumour margins (Barkan *et al.*, 1988).

Different criteria have been used to define the tumour mass before and after therapy in acromegalic patients. In some studies, a two-dimensional analysis has been performed (Gasperi *et al.*, 1993; Morange *et al.*, 1994), but with poor accuracy for evaluating small differences of tumour size (Lundin & Pedersen, 1992). In other reports, the parameter of evaluation has not been specified, making the comparison of results practically impossible (Marek *et al.*, 1994; Lancranjan *et al.*, 1996; Giusti *et al.*, 1997). According to previous studies (Arosio *et al.*, 1995; Caron *et al.*, 1997; Newman *et al.*, 1998), we performed a three-dimensional analysis which permits a more accurate estimation of pituitary size for intra- and interpatient comparisons (Lundin & Pedersen, 1992).

To our knowledge, this is the first study to compare the long-term effects of lanreotide SR and octreotide LAR® on tumour shrinkage during a 24-month follow-up period in newly diagnosed and previously untreated acromegalic patients. Both the analogues have shown comparable effects on tumour shrinkage, which was strictly related to the baseline tumour size. In particular, clinically significant shrinkage was observed only in patients with macroadenomas after 1 year of treatment, while shrinkage was not significant in patients with microadenomas. The latter patients, however, did not show any increase in tumour size during the entire study. Clearly, due to the lack of a placebo control group, we do not know whether pituitary tumour growth would have occurred in these patients without therapy.

The biochemical control of acromegaly was also different in patients with micro- and macroadenomas, but in an opposite way to the tumour shrinkage results. In fact, 'safe' GH levels (≤ 0.5 mU/l) were obtained in nine of 10 patients with microadenomas, while most patients with macroadenomas did not reach this therapeutic goal. The different effects of SMS-a on tumour shrinkage and GH hypersecretion could be explained by the different mechanisms that regulate the antimitotic and antisecretory

actions of SMS (Lamberts *et al.*, 1996). Indeed, the antisecretory effects of SMS-a are strictly linked to the reduction of intracellular cyclic AMP concentrations through the inhibition of adenylate cyclase (Lamberts *et al.*, 1996). On the contrary, the antimitotic action is related to the stimulation of tyrosine phosphatase activity, with inhibition of epidermal growth factor-receptor autophosphorylation, which regulates the cell proliferation (Lamberts *et al.*, 1996).

Lanreotide SR and octreotide LAR® had a comparable efficacy on the control of GH hypersecretion, as well as on tumour shrinkage. While other authors have studied the effects of octreotide LAR® in patients previously treated by lanreotide SR (Cozzi *et al.*, 1999; Turner *et al.*, 1999; Chanson *et al*., 2000), we evaluated the effects of the two drugs on different groups of newly diagnosed, previously untreated patients. The low number of enrolled patients permitted us neither to draw definite conclusions concerning the effectiveness of the two long-acting SMS-a nor to raise objections to the higher effectiveness of octreotide LAR® with respect to lanreotide SR recently demonstrated in a multicentre study (Chanson *et al*., 2000). It is likely that different dose titrations and frequencies of administration of the two drugs may be responsible for the different degrees of GH/IGF-I suppression reported in previous studies (Cozzi *et al.*, 1999; Turner *et al.*, 1999; Chanson *et al*., 2000).

The primary goal of therapy is the normalization of serum GH and IGF-I (Giustina *et al*., 2000), and tumour shrinkage is a beneficial additional effect of SMS-a, particularly when one is forced to use primary medical therapy due to patients' inability/unwillingness to undergo surgery. Therefore our study suggests that, in patients with macroadenomas, the lack of control of GH hypersecretion does not permit the use of SMS-a as a life-long primary therapy. However, the clearer cut and consistent shrinkage effect of both lanreotide SR and octreotide LAR® in these patients is critical in supporting their use before surgical intervention, the tumour size being one of the main determinants of neurosurgical failure and the incidence of postsurgery hypopituitarism (Newman *et al.*, 1998; Laws & Thapar, 1999). Therefore, an increase in the proportion of surgically controlled patients is likely to be obtained after tumour mass reduction. We suggest, however, that preoperative therapy should not last more than 12 months as our study demonstrated that no further shrinkage occurs after the first 12 months of therapy. In patients with microadenomas, good control of GH hypersecretion could permit the use of SMS-a for a longer period without, moreover, the risk of tumour growth. In these patients, however, medical therapy does not remove the source of GH hypersecretion and therefore cannot be considered as the most cost-effective therapeutic tool for every acromegalic patient with a pituitary microadenoma. In these patients, in fact, the neurosurgical approach in experienced hands provides up to a 90% chance of cure (Clayton, 1999). However, those patients with microadenomas who are unwilling to undergo surgery or are at very high risk can safely be given a primary long-term medical regimen with somatostatin analogues.

References

Arosio, M., Macchelli, S., Rossi, C.M., Casati, G., Biella, O. & Faglia, G. (1995) Effects of treatment with octreotide in acromegalic patients: a multicenter Italian study. *European Journal of Endocrinology*, **133**, 430–439.

Barkan, A.L., Lloyd, R.V., Chandler, W.F., Hatfield, M.K., Gebarski, S.S., Kelch, R.P. & Beitins, I.Z. (1988) Preoperative treatment of acromegaly with long-acting somatostatin analogue SMS 201-995: shrinkage of invasive pituitary macroadenomas and improved surgical remission rate. *Journal of Clinical Endocrinology and Metabolism*, **67**, 1040–1048.

Caron, P., Morange-Ramos, I., Cogne, M. & Jaquet, P. (1997) Three-year follow-up of acromegalic patients treated with intramuscular slow-release lanreotide. *Journal of Clinical Endocrinology and Metabolism*, **82**, 18–22.

Chanson, P., Boerlin, V., Ajzenberg, C., Bachelot, Y., Benito, P.L, Bringer, J., Caron, P., Charbonnel, B., Cortet, C., Delemer, B., Escobar-Jimenez, F., Foubert, L., Gaztamibide, S., Jockenhoevel, F., Kuhn, J.M., Leclere, J., Lorcy, Y., Pertemuter, L., Prestele, H., Roger, P., Rohmer, V., Santen, R., Sassolas, G., Schebaum, W.A., Schopohl, J. & Torres, E. (2000) Comparison of actrotide acetate LAR and lanreotide SR inpatients with acromegaly. *Clinical Endocrinology*, **53**, 577–586.

Clayton, R.N. (1999) How many surgeons to operate on acromegalic patients. *Clinical Endocrinology*, **50**, 557–559.

Cozzi, R., Dallabonzana, R., Attanasio, M., Barausse, M. & Oppizzi, G. (1999) A comparison between octreotide LAR and lanreotide SR in the chronic treatment of acromegaly. *European Journal of Endocrinology*, **141**, 267–271.

Davies, P.H., Stewart, S.E., Lancrajan, I., Sheppard, M.C. & Stewart, P.M. (1998) Long-term therapy with long-acting octreotide (Sandostatin® LAR®) for the management of acromegealy. *Clinical Endocrinology*, **48**, 311–316.

Di Chiro, G. & Nelson, K.B. (1962) The volume of the sella turcica. *American Journal of Radiology*, **87**, 989–1008.

Duncan, E. & Wass, J.A.H. (1999) Investigation protocol: acromegaly and its invetigation. *Clinical Endocrinology*, **50**, 285–293.

Ezzat, S., Snyder, P.J., Young, W.F., Boyajy, L.D., Newman, C., Klibanski, A., Molitich, M.E., Boyd, A.E., Sheeler, L., Cook, D.M., Malarkey, W.B., Jackson, I., LeeVance, M., Thorner, M.O., Barkan, A., Frohman, L.A. & Melmed, S. (1992) Octreotide treatment of acromegaly. A randomized multicenter study. *Annals of Internal Medicine*, **117**, 711–718.

Ferone, D., Colao, A., van der Lely, A.J. & Lambers, S.W.J. (2000) Pharmacotherapy or surgery as primary treatment for acromegaly. *Drugs Aging*, **17**, 81–92.

Flogstad, A.K., Halse, J., Bakke, S., Lancranjan, I., Marbach, P., Bruns, C. & Jervell, J. (1997) Sandostatin LAR in acromegalic patients: long-term treatment. *Journal of Clinical Endocrinology and Metabolism*, **82**, 23–28.

Freda, P. & Wardlaw, S.L. (1999) Diagnosis and treatment of pituitary tumours. *Journal of Clinical Endocrinology and Metabolism*, **84**, 3859–3866.

Gasperi, M., Petrini, L., Pilosu, R., Nardi, M., Marcello, A., Mastio, F., Bartalena, L. & Martino E. (1993) Octreotide treatment does not affect size of most non-functioning pituitary adenomas. *Journal of Endocrinological Investigation*, **16**, 541–543.

Gillis, J.C., Noble, S. & Goa, K.L. (1997) Octreotide long-acting release (LAR). *Drugs*, **53**, 681–699.

Giusti, M., Gussoni, G., Cuttica, G.M., Giordano, G. & the Italian Multicenter Slow Release Lanreotide Study Group. (1996) Effectiveness and tolerability of slow release lanreotide treatment in active acromegaly: 6-month report on an Italian multicenter study. *Journal of Clinical Endocrinology and Metabolism*, **81**, 2089–2097.

Giusti, M., Ciccarelli, E., Dallabonzana, D., Delitala, G., Faglia, G., Liuzzi, A., Gussone, G. & Giordano, G. (1997) Clinical results of long-term slow release lanreotide treatment of acromegaly. *European Journal of Clinical Investigation*, **27**, 277–284.

Giustina, A., Zaltieri, G., Negrini, F. & Wehrenber, W. (1996) The pharmacological aspects of the treatment of acromegaly. *Pharmacology Research*, **43**, 247–268.

Giustina, A., Barkan, A., Casanneva, F.F., Cavagnini, F., Frohman, L., Ho, K., Veldhuis, J., Wass, J., Von Werder, K. & Melemed, S. (2000) Criteria for cure of acromegaly: a consensus statement. *Journal of Clinical Endocrinology and Metabolism*, **85**, 526–529.

Lamberts, S.W.J., van der Lely, A.J., de Herder, W.W. & Hofland, L.J. (1996) Octreotide. *New England Journal of Medicine*, **25**, 246–254.

Lancranjan, C., Bruns, P., Grass, P., Jaquet, P., Jervell, J., Kendall-Taylor, P., Lamberts, S.W.J., Marbach, p., Orskov, H., Pagnani, G., Sheppard, M. & Simionescu, L. (1996) Sandostatin LAR: a promising therapeutic tool in the management of acromegalic patients. *Metabolism*, **45** (Suppl. 1), 67–71.

Laws, E.R. & Thapar, K. (1999) Pituitary surgery. *Endocrinology and Metabolism Clinics of North America*, **28**, 119–131.

Lundin, P. & Pedersen, F. (1992) Volume of pituitary macroadenomas: assessment by MRI. *Journal of Computer Assisted Tomography*, **16**, 519–524.

Marek, J., Hana, V., Krsek, M., Justova, V., Catus, F. & Thomas, F. (1994) Long-term treatment of acromegaly with the slow-relase somatostatin analogue lanreotide. *European Journal of Endocrinology*, **131**, 20–26.

Melmed, S., Jackson, I., Kleinberg, D. & Klibanski, A. (1998) Current treatment guidelines for acromegaly. *Journal of Clinical Endocrinology and Metabolism*, **83**, 2646–2652.

Morange, I., De Boisvilliers, F., Chanson, P., Lucas, B., Dewailly, D., Catus, F., Thomas, F. & Jaquet, P. (1994) Slow release lanreotide treatment in acromegalic patients previously normalized by octreotide. *Journal of Clinical Endocrinology and Metabolism*, **79**, 145–151.

Naidich, M.J. & Russel, E.J. (1999) Current approaches to imaging of the sellar region and pituitary. *Endocrinology and Metabolism Clinics of North America*, **28**, 45–79.

Newman, C.B., Melmed, S., George, A., Torigian, D., Duhaney, M., Snyder, P., Young, W., Klibanski, A., Molitch, M.E., Gagel, R., Sheeler, L., Cook, D., Malarkey, W., Jackson, I., Lee Vance, M., Barkan, A., Frohman, I. & Kleinberg, D.L. (1998) Octreotide as primary therapy for acromegaly. *Journal of Clinical Endocrinology and Metabolism*, **83**, 3034–3040.

Orme, S.M., McNailly, R.J.Q., Cartwright, R.A. & Belchetz, P.E. (1998) Mortality and cancer incidence in acromegaly: a retrospective cohort study. *Journal of Clinical Endocrinology and Metabolism*, **83**, 2730–2734.

Plewe, G., Beyer, J., Krause, U., Neufeld, M. & Del Pozo, E. (1984) Long-acting and selective suppression of growth hormone secretion by somatostatin analogue SMS 201-995 in acromegaly. *Lancet*, **2**, 782–784.

Stewart, P.M., Kane, K.F., Stewart, S.E., Lancranjan, I. & Sheppard, M.C. (1995) Depot long-acting somatostatin analogue (Sandostatin-LAR) is an effective treeatment for acromegaly. *Journal of Clinical Endocrinology and Metabolism*, **80**, 3267–3272.

Turner, H.E., Vadivale, A., Keenan, J. & Wass, J.A.H. (1999) A comparison of lanreotide and octreoide LAR® for treatment of acromegaly. *Clinical Endocrinology*, **51**, 275–280.