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Primary Medical Therapy for Acromegaly: An Open, Prospective, Multicenter Study of the Effects of Subcutaneous and Intramuscular Slow-Release Octreotide on Growth Hormone, Insulin-Like Growth Factor-I, and Tumor Size

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Conventional surgery and radiotherapy for acromegaly have limitations. There are few data on the use of the somatostatin analog octreotide (Oct) as primary medical therapy. An open prospective study of 27 patients with newly diagnosed acromegaly was conducted in nine endocrine centers in the United Kingdom. Twenty patients had macroadenomas, and 7 had microadenomas. For the first 24 wk (phase 1), patients received sc Oct in an initial dose of 100 μg, 3 times daily, increased to 200 μg three times daily after 4 wk in the 13 patients whose mean serum GH remained greater than 5 mU/liter (2 μg/liter). Five-point GH profiles were performed at 0, 4, 12, and 24 wk, and high resolution pituitary imaging using a standard protocol was performed at 0, 12, and 24 wk (magnetic resonance imaging in 25 patients and computed tomography in 2). Tumor dimensions and volumes were calculated by a central, reporting neuroradiologist, and the results were audited by a second, independent neuroradiologist. After 24 wk, 15 patients proceeded to phase 2 of the study with a direct switch to monthly injections of the depot formulation of Oct, Sandostatin long-acting release (Oct-LAR). Further GH profiles were performed at 36 and 48 wk, and pituitary imaging was performed at 48 wk.

The median pretreatment serum GH concentration was 30.7 mU/liter (range, 6.7–141.4). During sc Oct, serum GH fell to less than 5 mU/liter in 9 patients (38%), and IGF-I fell to normal in 8 patients (33%). All 27 tumors shrank during sc Oct; for microadenomas the median tumor volume reduction was 49% (range, 12–73), and for macroadenomas it was 43% (range, 6–92). After 24 wk of Oct-LAR (end of phase 2), the GH level was less than 5 mU/liter in 11 of 14 patients (79%), and IGF-I was normal in 8 of 15 patients (53%). In the 15 patients given Oct-LAR (10 macroadenomas), wk 48 scans showed a further overall median tumor volume reduction of 24%. At the end of the study 79% of patients had mean serum GH levels below 5 mU/liter, 53% had normal IGF-I levels, and 73% showed greater than 30% tumor shrinkage. Twenty-nine percent of patients achieved all 3 targets, but no patient with pretreatment GH levels above 50 mU/liter did so at any stage of the study.

Primary medical therapy with Oct offers the prospect of normalization of GH/IGF-I levels together with substantial tumor shrinkage in a significant subset of acromegalic patients. This is most likely to occur in patients with pretreatment GH levels less than 50 mU/liter (20 μg/liter). (*J Clin Endocrinol Metab* 87: 4554–4563, 2002)

THE OVERALL STRATEGY for the management of acromegaly has altered little in the past 30 yr. Most patients receive surgery as primary therapy, usually via the transsphenoidal route, followed by external pituitary radiotherapy in those with residual GH excess. Interim medical treatment with somatostatin analogs or dopamine agonists is given until serum GH and IGF-I fall to the safe levels now known to be associated with reversal of the increased mortality associated with untreated acromegaly (1). Most clinicians accept that this traditional management approach has limitations.

Although transsphenoidal surgery by an experienced operator may lower GH to safe levels (<5 mU/liter, <2 μg/liter) in about 90% of patients with microadenomas (2–4), this tumor size is present in only 20–30% of newly diagnosed acromegalics (5). Surgical remission rates are considerably lower for patients with larger tumors. More than 50% of patients with tumors more than 2 cm in diameter and with extrasellar extension will still have unacceptably high postoperative GH levels (3). Pretreatment with somatostatin an-

Abbreviations: LAR, Long-acting release; MRI, magnetic resonance imaging; Oct, octreotide.

alogs may improve surgical outcome for some tumors with limited invasiveness, but such therapy does not enable cure of lesions with major invasion (4, 6). As with other pituitary tumor types, several large series report a long-term relapse rate of up to 10% in patients cured initially by surgery (7). External radiotherapy can be an effective adjunctive treatment, but often takes several years to normalize serum GH and IGF-I levels, particularly if the pretreatment GH levels are above 20 mU/liter (8 μg/liter). Many patients acquire varying degrees of anterior hypopituitarism as a result of irradiation, including some with clinically significant GH deficiency (8).

Several early studies suggested that somatostatin analog therapy induces a degree of tumor regression in a proportion of patients with GH-secreting adenomas (9–11). However, many of these patients had received previous surgery and/or radiotherapy, and the consequent fibrosis may have limited their potential for tumor shrinkage with medical therapy. There have been few previous studies of primary somatostatin analog therapy in patients with newly diagnosed and untreated acromegaly. The first demonstration of tumor shrinkage in *de novo* acromegaly was in two patients given octreotide (Oct) by continuous sc infusion (12). Lundin *et al.* described the results of sc Oct therapy in 17 *de novo* patients studied mostly with magnetic resonance imaging (MRI) (13). Although a mean tumor volume reduction of 51% was demonstrated in 11 patients with analyzable scans, and the mean serum GH concentration fell to less than 10 mU/liter in 67% of patients, serum IGF-I was normalized in only 28%. In contrast, only 3 of 13 newly diagnosed acromegalics treated with sc Oct, whose retrospective MRI data were reported by Newman *et al.* (14), showed more than 25% tumor volume reduction, although serum IGF-I fell to normal in 68% of these patients. A further cohort of 36 acromegalics treated with depot Oct, 15 of whom were *de novo* patients, has been reported recently by Colao *et al.* (15). All of the *de novo* patients showed tumor shrinkage (mean reduction, 53%; range, 18–100%). However, shrinkage was less evident in the previously operated patients; none could be demonstrated in 4 of 9 patients evaluated using serial MRI.

The United Kingdom Primary Octreotide Therapy Study Group was established to address some of these uncertainties. We report the results of a prospective, multicenter study of sc, followed by im slow-release Oct given as primary medical therapy to a group of 27 patients with newly diagnosed acromegaly. An important feature of this study was the centralized imaging analysis of the high resolution MRI scans carried out using an accepted protocol together with independent neuroradiological audit of the tumor volume data. The study demonstrates that a significant subset of newly diagnosed patients can achieve lowering of serum GH to less than 5 mU/liter (2 μg/liter), normalization of serum IGF-I, and tumor shrinkage with primary Oct therapy alone.

Subjects and Methods

Patients

Patients with newly diagnosed acromegaly were recruited from nine regional endocrine centers in the United Kingdom. All had biochemically active disease, with a mean serum GH concentration greater than 5 mU/liter (2 μg/liter) that failed to suppress below 2 mU/liter (0.8 μg/liter) after oral administration of 75 g glucose and had an adenoma visible on pituitary imaging. No patient had received previous surgery, radiotherapy, or medical therapy with somatostatin analogs or dopamine agonists. Patients with optic chiasmal compression were excluded. Twenty-seven patients fulfilled these criteria and were suitable for the study (17 men and 10 women; mean age, 53 yr; range, 21–73 yr). All were Caucasian. The mean duration of symptoms before diagnosis was 98 months (range, 6–261 months). The study protocol was approved by ethical committees at each of the centers, and each patient gave written informed consent.

Study design

The study comprised 2 phases, each lasting 24 wk. In phase 1 all patients commenced sc Oct in a dose of 100 μg three times daily (aiming for 8 h between each injection). After 4 wk, the dose was increased to 200 μg three times daily if the mean serum GH concentration remained above 5 mU/liter; 13 of 27 patients progressed to the higher dose. In phase 2, patients were switched from sc Oct to the im depot preparation, Sandostatin-LAR (long-acting release), without a washout period. Fifteen patients completed phase 2. Ten received Sandostatin-LAR (20 mg) by deep im injection into the gluteal muscles at 4-wk intervals for a total of 6 injections. The remaining 5 (all of whom had received 200 μg Oct, sc, three times daily during phase 1) received higher doses of Sandostatin-LAR. Three patients received 6 injections of 30 mg (patients 3, 14, and 19; Fig. 1), and 2 received 2 20-mg injections, followed by 4 30-mg injections (patients 15 and 22; Fig. 1). Three centers decided at the outset of the study to refer their patients for surgery at the end of phase 1 (8 patients), whereas 5 centers entered all of their patients into phase 2 (13 patients). In the remaining center, 4 of 6 patients were referred for surgery after phase 1, and 2 entered phase 2; these decisions were made solely on the basis of patient preference and not their tumor responses to Oct during phase 1. The percentages of patients with microadenomas were similar in phase 1 (26%) and phase 2 (33%).

GH and IGF-I measurements

Five-point serum GH profiles were performed at baseline and at wk 4, 12, 24, 36, and 48. Patients attended the endocrine clinic, fasting, between 0800 and 0900 h, and an iv cannula was inserted, which was kept patent using heparinized saline. Blood samples were obtained at baseline and at hourly intervals for 4 h. A light breakfast was offered after the fasting blood sample had been drawn. At the initial study visit the first sc injection of Oct was administered after the GH profile had been completed, but at wk 4, 12, and 24, an sc injection of Oct was administered after the basal blood sample had been collected. In phase 2, Sandostatin-LAR injections were administered after the GH profiles had been completed. A fasting serum sample for IGF-I determination was obtained at baseline and at wk 4, 12, 24, 36, and 48. Serum was separated and stored at −20 C until transported for GH and IGF-I analysis at a central laboratory (Cardiological Sciences Analytical Unit, St. George's Hospital, London, UK). In three patients, GH and IGF-I concentrations were inadvertently measured using local assays, and only their MRI data are reported. Serum for GH determination at wk 48 was missing for patient 12.

Serum GH was measured using a chemiluminescent immunometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA). Samples were measured against GH standard WHO 80/505, and intra- and inter-assay coefficients of variation were 4% and 9.2%, respectively, at a GH concentration of 20 mU/liter. In this assay a GH concentration of 2.5 mU/liter is equivalent to 1 μg/liter. Serum IGF-I was measured using an immunoradiometric assay (Nichols Institute Diagnostics). Recombinant IGF-I standards were calibrated against WHO 87/518, and intra- and interassay coefficients of variation were less than 5% and less than 8%, respectively, at IGF-I concentrations between 60 and 1040 μg/liter. The age-related reference ranges (mean ± 2 SD) for serum IGF-I in adult men and women were 122–400 μg/liter (19–39 yr), 75–306 (40–54 yr), and 48–225 (≥55 yr).

Clinical assessments

At each visit patients were asked to score various symptoms of acromegaly (headache, sweating, fatigue, arthralgia, carpal tunnel

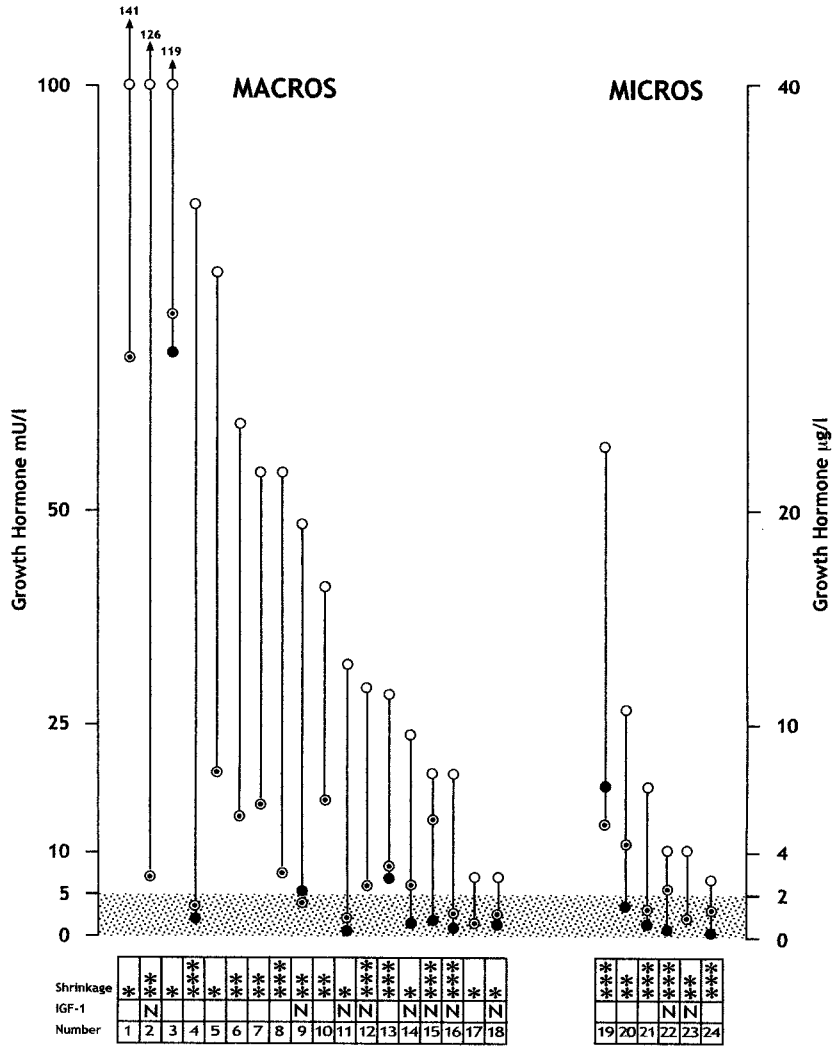

FIG. 1. Mean serum GH responses to Oct therapy in 18 patients with GH-secreting macroadenomas (*left panel*; patients 1–18) and 6 patients with GH-secreting microadenomas (*right panel*; patients 19–24). ○, GH level at baseline; ⊙, GH level at 24 wk (the end of phase 1); ●, GH level at 48 wk (the end of phase 2). The latter symbol identifies 14 patients who completed phase 2; the 15th (patient 12) had missing wk 48 GH data. GH hormone concentrations are shown in both milliunits per liter and microunits per liter, and the *shading* indicates levels less than 5 mU/liter (2 μg/liter). *Asterisks* indicate the amount of tumor shrinkage at latest assessment (*, <30%; **, 30–60%; ***, >60% tumor volume reduction). N, Normal age-related IGF-I concentration at latest assessment.

syndrome, and snoring) using a five-point scale, where 0 = not present, 1 = mild, 2 = moderate, 3 = severe but not disabling, and 4 = severe and incapacitating. Physical examination, including blood pressure measurement, was performed at 0, 12, 24, 36, and 48 wk. Adverse events were recorded, including any local injection site reactions.

MRI and tumor volume calculations

Pituitary imaging was performed at baseline before any treatment and at wk 12, 24, and 48. Most patients underwent MRI, but high resolution computed tomography was used in two patients who were unable to tolerate MRI (patients 5 and 19 in Fig. 1). High resolution MRI used scanners of at least 1.0T field strength. Using MRI, T1-weighted, thin section (3 mm thick, with 0.1 distance factor interleaved), sagittal and coronal images of the pituitary were obtained before and after iv gadolinium. The centers attempted to place the patient in the same position for imaging on each occasion and to obtain slices in as similar a position as possible. All parameters were kept constant for each imaging session, and the sequences were optimized by each local neuroradiologist for their scanner. Magnified views of the pituitary region were printed onto film and sent to the central reporting neuroradiologist (J.W.). Where possible, scans were also sent electronically. The order of scan measurements was made randomly for each patient, although all scans for each patient were measured in a single session. All neuroradiological measurements were made blind to the clinical and endocrine data. Measurements of maximum pituitary tumor diameters were taken in the coronal, sagittal, and axial planes and corrected for magnification factor. The shape of the tumor was noted (sphere, ovoid, cuboid, cone, *etc.*), and the volume was calculated using the corresponding mathematical formula. The percent change in tumor volume from baseline was calculated. Various alternative measurement methods were tested (*e.g.* point counting, stereology, and electronic measurement of tumor area multiplied by slice thickness), but were found to be inferior.

In view of the observer subjectivity inherent in the technique, especially when tumors are small, irregular, or have indistinct margins (16), a second radiologist (E.T.) conducted an independent, blinded audit of the measurements. In cases where there were substantial differences (defined as >20% difference in change in tumor volume), the 2 neuroradiologists re-reviewed the scans together and agreed upon the final volume determination. There were 9 such disagreements from a total of 92 tumor volume changes. All were due to awkward tumor shapes, different magnification factors between imaging sessions, and different scan orientations. Although centers attempted to keep the position and slice orientation constant, the small size of the lesions and frequently irregular shape meant that in some cases even minor changes in slice orientation had the potential to affect the measurements. Resolution of the discrepancies resulted in 6 alterations to the original calculations (1 each at baseline and 12 wk, and 2 each at 24 and 48 wk). The final imaging dataset contained the 6 changes agreed after independent audit. Spearman rank correlation coefficients were 0.95, 0.91, and 0.97 for the volume calculations by the 2 radiologists at baseline, 24 wk, and 48 wk, respectively, (all $P = 0.0001$).

Safety variables

Blood was obtained for fasting glucose concentration, routine biochemistry including liver function tests, and full blood count at baseline, 24 wk, and 48 wk. Biliary ultrasonography was performed during the 3 months before study entry and again at 24 and 48 wk.

Statistical analysis

The serum GH concentration at each study visit was expressed as the mean value obtained during a 5-point profile. Percent differences in serum GH concentrations during phases 1 and 2 of the study were not normally distributed and were analyzed using the Wilcoxon rank-sum test. Percent changes in tumor volumes were normally distributed and were analyzed using paired *t* test. The relationship between percent tumor shrinkage and percent GH reduction was determined by calculation of the Spearman rank correlation coefficient. Changes in symptom scores for the 27 patients who completed phase 1 and the 15 who completed the entire study were assessed using the Kruskal-Wallis test. $P < 0.05$ was assumed to indicate statistical significance in all tests.

Results

Effects of Oct on serum GH concentration

Serum GH and IGF-I measurements are available for 24 patients. The median serum GH concentration for all 24 patients was 30.7 mU/liter (range, 6.7–141.4), with a value of 44.8 mU/liter for the 18 patients with macroadenomas and 13.8 mU/liter for the 6 with microadenomas. Oct induced a significant fall in serum GH in all patients, as shown in Fig. 1. During phase 1, the median GH level fell from 30.7 to 6.4 mU/liter ($P < 0.0001$), with significant falls in patients with both macro- and microadenomas (Table 1). At the end of phase 1, mean serum GH had fallen to less than 5 mU/liter in 9 of 24 patients (38%), 6 with macroadenomas and 3 with microadenomas.

The patients were divided into those who remained in the study until wk 48 and those who withdrew at 24 wk to assess whether there was any difference between the two subgroups in terms of their biochemical parameters at the end of phase 1 (Table 1). Patients with macroadenomas withdrawing at 24 wk had mean serum GH concentrations similar to those continuing in the study ($P = 0.0832$). Only one patient with a microadenoma withdrew at 24 wk; his mean serum GH concentration was 1.8 mU/liter, lower than the minimum value for the group continuing to phase 2.

The 24-patient population was stratified according to pretreatment serum GH concentrations, and the number of patients in each of the subgroups (<25, 25–50, and >50 mU/liter) and the percentage of patients with GH normalization during Oct are shown in Table 2. There was a clear trend toward a more satisfactory Oct response for patients with lower GH levels at study entry; all patients with initial GH levels less than 25 mU/liter showed GH normalization after 48 wk compared with 75% of patients with initial GH between 25–50 mU/liter and only 33% of patients with initial GH levels greater than 50 mU/liter. The 2 patients with the highest GH levels at the end of phase 1 had some of the highest pretreatment values (patients 1 and 3; Fig. 1).

During phase 2 there was a further fall in median GH from 6.4 to 1.8 mU/liter ($P = 0.0031$; Fig. 1 and Table 1). For some patients there was little further fall in GH, whereas others showed appreciable reduction (*e.g.* patients 15 and 20; Fig. 1). Seventy-nine percent of patients had mean serum GH levels below 5 mU/liter by the end of phase 2.

Effects of Oct on serum IGF-I concentration

The median serum IGF-I concentration was higher in patients with macroadenomas (718 μg/liter) than in those with microadenomas (532 μg/liter), although there was some overlap between the 2 groups (Table 1). At the end of phase 1, serum IGF-I fell to within the age-related normal range in 8 of 24 patients (33%) compared with 9 of 24 (38%) who had GH concentrations below 5 mU/liter at this stage. Of the 15 patients who completed phase 2, 8 had normal serum IGF-I concentrations (53%), 7 of whom also had mean serum GH levels below 5 mU/liter. Figure 2 shows that 12 of 15 patients (80%) had serum IGF-I concentrations below 300 μg/liter at the end of phase 2.

As described above, the patients were divided into those who remained in the study until wk 48 and those who withdrew at 24 wk. There was a statistically significant difference between the two groups ($P = 0.0088$), with the median and minimum IGF-I values being 50% higher in the group of patients with macroadenomas who withdrew, although the maximum values were similar [median (range), 626 μg/liter (329–720) for those who withdrew and 250 μg/liter (162–730) for those who continued]. Only one patient with a microadenoma withdrew at 24 wk; his IGF-I level was 213 μg/liter, lower than the minimum value for the group continuing to phase 2.

Serum IGF-I responses to Oct were related to the pretreatment GH concentrations (Table 2). At 48 wk, 71% of patients

TABLE 1. Serum GH and IGF-I concentrations in patients with GH-secreting macro- and microadenomas before and after Oct

		Baseline	24 wk	24 wk[g]	48 wk
Macroadenomas (n)		18	18	10	9
GH (mU/liter)	Median	44.8	7.1[a]	5.0[b]	1.9[e]
	Range	6.7–141.4	1.3–73.1	1.3–73.1	0.8–68.5
IGF-I (μg/liter)	Median	718	360[a]	250[c]	236[f]
	Range	444–1411	162–730	162–730	185–470
Microadenomas (n)		6	6	5	5
GH (mU/liter)	Median	13.8	4.3[d]	5.4[f]	1.4[f]
	Range	6.8–57.5	1.8–13.1	2.9–13.1	0.6–17.4
IGF-I (μg/liter)	Median	532	257[d]	263[f]	243[f]
	Range	386–780	213–420	235–420	173–342

[a] $P < 0.0001$; [b] $P = 0.0020$; [c] $P = 0.0039$; [d] $P = 0.0313$, compared with respective baseline values; and [e] $P = 0.0195$, [f]NS, compared with respective wk 24 values.

[g] Patients continuing to phase 2 of the study at 24 wk.

TABLE 2. Success rates stratified by pretreatment serum GH concentration

Pretreatment GH level	GH and IGF-I responses	At 24 wk	At 48 wk
<25 mU/liter	Normalized GH (<5 mU/liter)	6/9 (67%)	7/7 (100%)
	Normalized IGF-I	4/9 (44%)	5/7 (71%)
	Normalized GH and IGF-I	2/9 (22%)	5/7 (71%)
25–50 mU/liter	Normalized GH	2/6 (33%)	3/4 (75%)
	Normalized IGF-I	3/6 (50%)	3/5 (60%)
	Normalized GH and IGF-I	2/6 (33%)	2/4 (50%)
>50 mU/liter	Normalized GH	1/9 (11%)	1/3 (33%)
	Normalized IGF-I	1/9 (11%)	0/3 (0%)
	Normalized GH and IGF-I	0/9 (0%)	0/3 (0%)

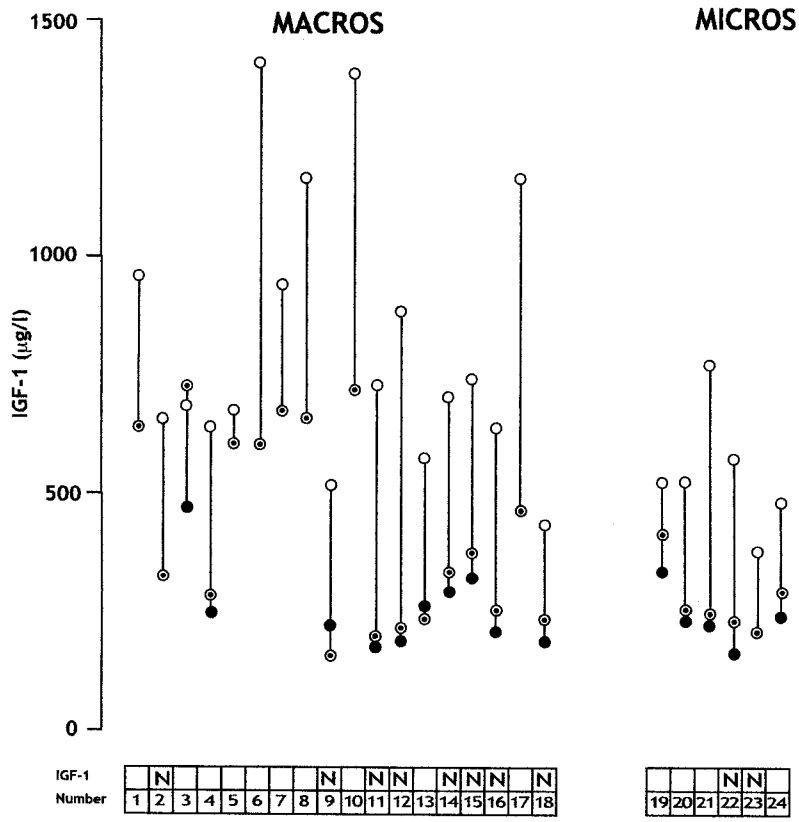

FIG. 2. Serum IGF-I responses to Oct therapy in 18 patients with GH-secreting macroadenomas (*left panel*; patients 1–18) and 6 patients with GH-secreting microadenomas (*right panel*; patients 19–24). ○, IGF-I level at baseline; ⊙, IGF-I level at 24 wk (the end of phase 1); ●, IGF-I level at 48 wk (the end of phase 2). N, Normal age-related IGF-I concentration at latest assessment.

with initial GH levels less than 25 mU/liter had IGF-I normalization compared with 60% of patients with initial GH between 25–50 mU/liter and none with initial GH levels greater than 50 mU/liter.

Effects of Oct on tumor volume

At baseline the median maximal tumor diameter was 14 mm (range, 5–46 mm), and tumor volume was 918 mm^3 (range, 169–61,733 mm^3); there were 20 macroadenomas (maximum diameter, >10 mm) and 7 microadenomas (maximum diameter, <10 mm; Table 3). Importantly, there were no statistically significant differences in tumor volume or coronal diameter between patients withdrawing at 24 wk and those continuing into phase 2 ($P = 0.2892$ and $P = 0.0965$). Three of the tumors were very large (patient 6, 61,733 mm^3; patient 1, 27,600 mm^3; patient 3, 14,540 mm^3). All 27 tumors shrank after treatment with Oct. The amount of shrinkage was more than 10% in all but 1 patient (patient 3; *top graph* in Fig. 3B). At 24 wk the macroadenomas showed significant volume reduction by a median of 43% (range, 6–92%), and the microadenomas by a median of 49% (range, 12–73%; Table 3). In fact, significant tumor regression had already taken place by wk 12 (Fig. 3).

During phase 2 there was further overall median tumor volume reduction of 24% (Table 3 and Fig. 3); 10 showed definite further shrinkage (6 macroadenomas), 4 showed no change (3 macroadenomas), and 1 showed a slight increase. The latter patient (no. 20) had a pretreatment tumor volume of 763 mm^3, which fell to 730 mm^3 at 12 wk and to 523 mm^3 at 24 wk during sc Oct (100 μg three times daily) and then rose to 635 mm^3 at 48 wk during treatment with Sandostatin-LAR (20 mg every 4 wk). Figure 1 shows that 7 of 20 macroadenomas (35%) and 5 of 7 microadenomas (71%) shrank by over 60% during the study. Some representative MRI images demonstrating microadenoma and macroadenoma shrinkage are shown in Figs. 4 and 5. There was only a weak

TABLE 3. Tumor dimensions and volumes before and after Oct

	Baseline	12 wk	24 wk	24 wk[j]	48 wk
Macroadenomas (n)	20	20	20	10	10
Volume (mm^3)					
Median	1824	980[a]	939[a]	613[i]	368[b]
Range	474–61,733	167–46,997	63–29,537	63–13,343	22–14,278
Coronal diameter (mm)					
Median	14.7	13.6[c]	12.4[a]	10.1[f]	8.4[d]
Range	8.5–46.0	7.4–43.5	6.8–42.8	6.8–28.0	4.0–26.0
Microadenomas (n)	7	7	7	5	5
Volume (mm^3)					
Median	255	205[a]	118[e]	171[f]	113[a]
Range	169–435	133–333	58–344	73–344	60–180
Coronal diameter (mm)					
Median	9.2	8.5[f]	7.8[g]	8.0[f]	7.0[h]
Range	4.8–9.8	3.5–9.7	2.8–8.9	5.4–8.9	4.5–8.1

[a] $P < 0.0001$; [b] $P = 0.0012$; [c] $P = 0.0004$; [d] $P = 0.0042$; [e] $P = 0.001$; [f] NS; [g] $P = 0.0249$; [h] $P = 0.0081$; [i] $P = 0.0448$, compared with respective baseline values (paired t tests). Sagittal and axial measurements were also made, but only the coronal readings are shown.

[j] Patients continuing to phase 2 of the study at 24 wk. There was no statistically significant difference in tumor volume or coronal diameter between patients withdrawing at 24 wk and those continuing ($P = 0.2892$ and $P = 0.0965$, t test).

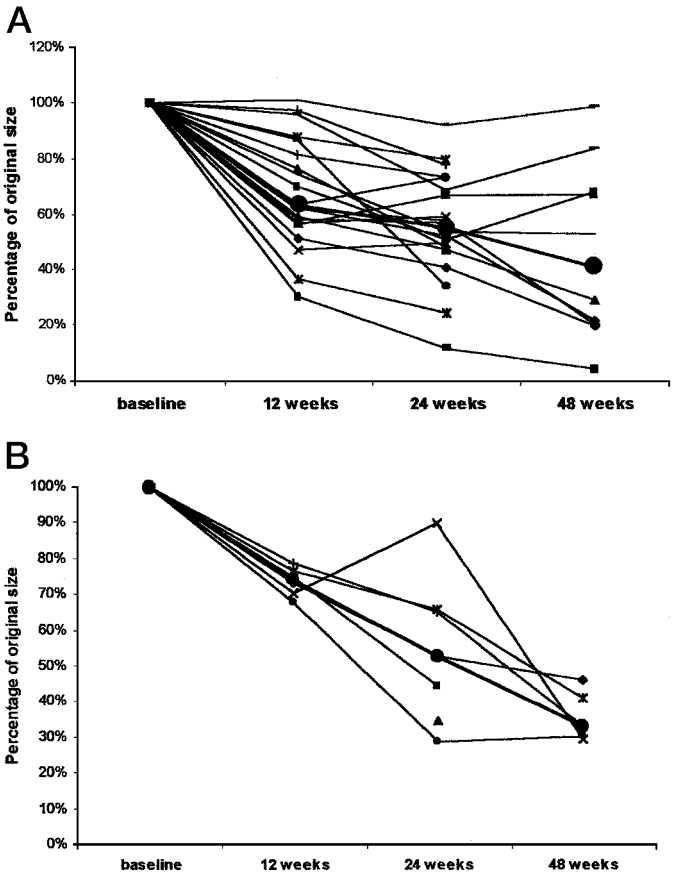

FIG. 3. Tumor volume changes after Oct therapy expressed as a percentage of the pretreatment volume in 20 macroadenomas (A) and 7 microadenomas (B). The *thick lines* and *larger symbols* in each panel indicate the mean values for each tumor group.

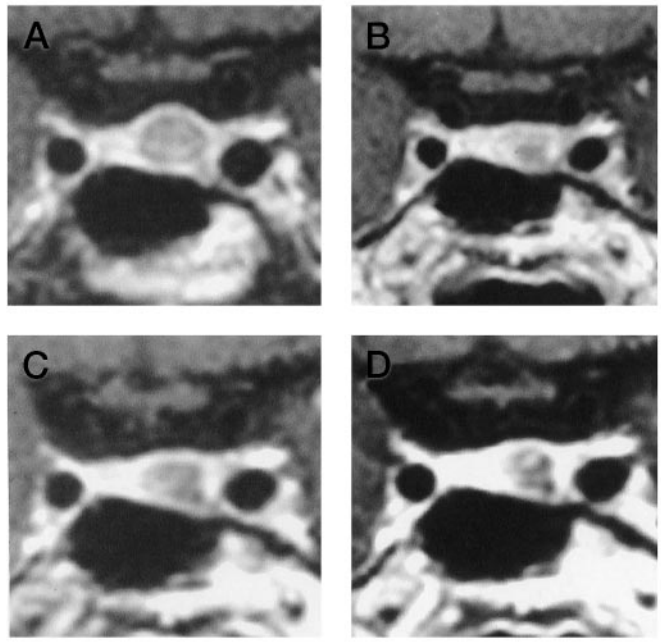

FIG. 4. Representative MRI images demonstrating shrinkage of a microadenoma (patient 20). The four frames show coronal images at baseline (A) and after 12 wk (residual volume, 73%; B), 24 wk (residual volume, 53%; C), and 48 wk (residual volume, 46%; D) of Oct therapy. At the end of phase 2, serum GH had fallen from 26.7 to 3.6 mU/liter, and IGF-I from 531 to 245 μg/liter.

correlation between the degree of tumor regression and the degree of GH suppression at the end of phase 1 ($r = 0.32$; $P = 0.129$). The time courses for the anatomical and biochemical responses are shown in Fig. 6. Although much of the GH suppression had already taken place by 12 wk, tumor shrinkage continued throughout the 1-yr study.

Symptomatic responses (Table 4)

Oct therapy produced significant improvements in several symptoms of acromegaly, particularly sweating and snoring. Headache and arthralgia were not prominent symptoms in this cohort of acromegalic patients; 21 of 27 and 25 of 27, respectively, scored these symptoms at 0–1 on study entry.

Effects of tumor shrinkage on other anterior pituitary function

This was not a primary objective of the United Kingdom Primary Octreotide Therapy Study, and serial dynamic pi-

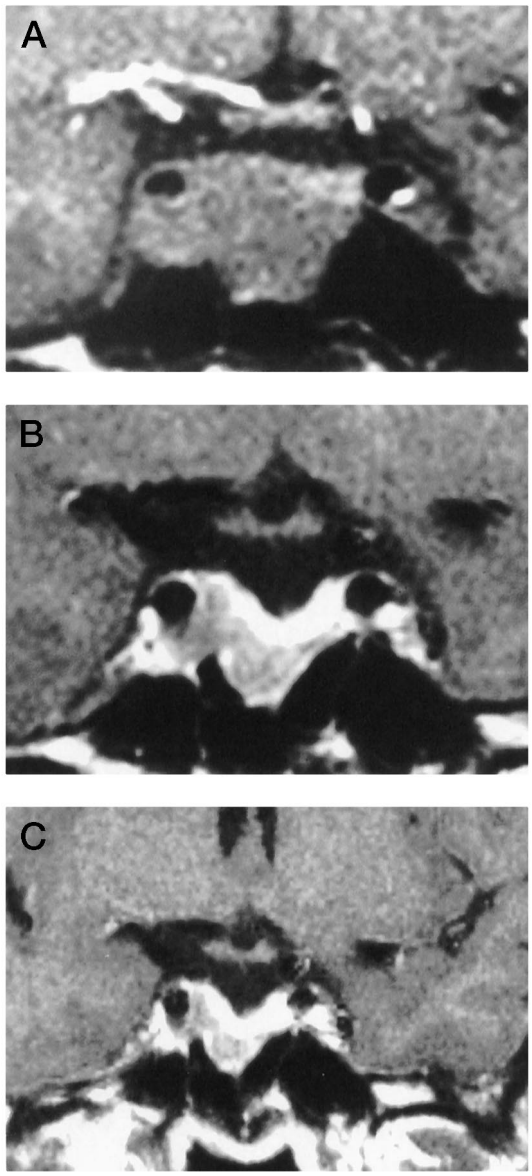

FIG. 5. Representative MRI images demonstrating shrinkage of a macroadenoma (patient 10). The three frames show coronal images at baseline (A) and after 12 wk (residual volume, 47%; B) and 24 wk (residual volume, 49%; C) of Oct therapy. At the end of phase 1, serum GH had fallen from 41.2 to 15.8 mU/liter, and IGF-I from 1388 to 720 μg/liter.

tuitary function testing was not performed. However, stored sera from most of the study patients were tested retrospectively for free T_4 and cortisol (0800–0900 h) in both sexes and for testosterone in men. Overall, there were no significant changes, even in those patients with more than 30% tumor shrinkage. No patient had an early morning cortisol level below 200 nmol/liter at any time during the study. Twenty-two patients maintained normal free T_4 concentrations, and one was mildly thyrotoxic (toxic multinodular goiter) throughout the study. Patient 24 had a subnormal free T_4 level of 9 pmol/liter before Oct, which had risen to 25 pmol/liter after 48 wk. Serum testosterone rose from 7.6 to 11.1 nmol/liter in patient 12 whose macroadenoma shrank by

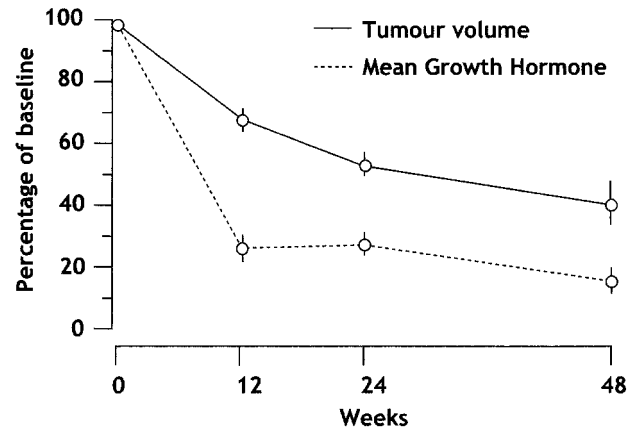

FIG. 6. Time courses for tumor shrinkage and GH suppression. Similar profiles were obtained when patients with macro- and microadenomas were plotted separately. Data points indicate the mean ± SEM.

73%. Eight men maintained normal testosterone levels, and 6 remained hypogonadal throughout the study.

Tolerability of Oct

Both the sc and depot formulations of Oct had good local tolerability and general patient acceptability. Only 4 of 14,692 sc and 3 of 90 im injections were associated with moderate to severe local injection site reactions (pain, erythema, or swelling). No patient withdrew from the study because of Oct adverse effects. There were no significant changes in routine biochemistry and hematology. Gallstones were demonstrated at baseline in 5 of the 27 patients. Twenty-six percent of patients showed new biliary ultrasonographic abnormalities during phase 1 (sludge or stones), with little overall change during phase 2. No patient developed biliary symptoms.

Discussion

The most important outcome from this study of primary Oct therapy in newly diagnosed acromegaly is the demonstration that significant tumor regression occurs in virtually all patients. Taken together with the results of other studies of primary medical therapy (13–15), this suggests that it may be appropriate to reconsider the traditional management algorithm for acromegaly. By analogy, the management of prolactinoma has been revolutionized in recent years by the introduction of primary medical therapy. Dopamine agonist drugs are now used as sole therapy for most patients, with surgery reserved for a small minority. Ninety percent of patients with macroprolactinomas can be expected to show at least 25% tumor shrinkage, and the use of external radiotherapy has declined (17). An ideal pituitary tumor therapy should enable control of tumor growth and size, relieve tumor pressure effects, and restore pituitary hormone levels to normal. It should also be safe, have good tolerability, and be cost-effective. The present study addressed whether Oct represents such a therapy for acromegaly.

Tumor shrinkage

On the average, both microadenomas and macroadenomas regressed to almost half the pretreatment size after 24 wk

of Oct therapy. Furthermore, it is clear that much of this volume reduction had already occurred by 12 wk (Fig. 3), but we do not have MRI data between baseline and 12 wk to support the possible use of primary Oct therapy in *de novo* patients with optic chiasmal compression. At the end of phase 2 the median tumor volume reduction was 61%.

In agreement with these results, Lundin *et al.* (13) found a mean tumor volume reduction of 51% in 11 *de novo* patients treated with sc Oct for up to 70 months and commented that most shrinkage took place during the first year of treatment. In contrast, Newman *et al*. (14) demonstrated tumor regression of more than 25% in only 3 of 13 patients treated with either 300 or 750 μg Oct, sc, daily for 6 months. However, this was a retrospective analysis of MRI scans at baseline and 6 months only, and the difficulties associated with sequential MRI scan analysis have already been emphasized in *Subjects and Methods*.

Colao *et al.* (15) studied 15 patients with *de novo* acromegaly treated with Oct-LAR every 28 d for 2 yr; 12 had macroadenomas and 3 had microadenomas. At the end of their study 7 patients were taking 20 mg, 6 were taking 30 mg, and 2 were taking 40 mg strength Oct-LAR injections. MRI scans were performed before and after 3, 6, 12, and 24 months of therapy. All 15 tumors decreased in size, with a mean volume reduction of 53% after 1 yr (range, 18–100%), results very similar to our own. There was little further reduction during the second year of therapy. These investigators also studied 9 patients treated with Oct-LAR after noncurative pituitary surgery, with MRI scans before and after 12 and 24 months of Oct therapy. For this group, data were confined to changes in maximal tumor diameter, presumably because of distortion of sellar anatomy and awkward tumor shapes after surgery. Notably, 4 of these patients showed no reduction in size with Oct-LAR despite a significant biochemical improvement. This is consistent with the results of previous studies of sc Oct and Oct-LAR, many conducted on patients with previous surgery and/or radiotherapy, which reported tumor regression in 29–72% of patients (10, 18). It is possible that fibrotic or other histological changes in the tumor remnant after surgical or radiotherapeutic interventions explain the less impressive changes in tumor size during somatostatin analog treatment. We reemphasize that none of the 27 patients in our study had received any form of previous therapy. Furthermore, the MRI analysis of our patients was more detailed than in any previous study, none of which has been subjected to independent audit of the imaging results.

TABLE 4. Symptomatic responses to Oct

	Baseline to 24 wk (n = 27)	Baseline to 48 wk (n = 15)
Headache	0.267	1.000
Fatigue	0.103	0.086
Sweating	0.001[a]	0.001[a]
Arthralgia	0.698	1.000
Carpal tunnel syndrome	0.027[a]	0.169
Snoring	0.002[a]	0.031[a]

[a] Statistical significance; *P* values derived using Kruskal-Wallis test.

Control of serum GH and IGF-I levels

There is now compelling evidence that lowering serum GH levels to less than 5 mU/liter (2–2.5 μg/liter) reverses the increased mortality associated with acromegaly, and this provides a useful biochemical target for therapeutic intervention (1, 2, 19). Similarly, normalization of serum IGF-I has been shown to correlate with improved life expectancy, although the evidence base is more limited than for GH (2). In our study the GH target was achieved in 38% of patients at the end of phase 1, rising to 79% at the end of phase 2. However, we should emphasize that our study was not a randomized comparison of sc and im slow-release Oct, and therefore no conclusions can be drawn about the relative efficacy of each formulation. Lundin *et al.* (13) reported GH levels less than 10 mU/liter in 67% of their patients. Nadir serum GH levels of 2.5 μg/liter or less were found by Colao *et al.* (15) in 73% of 15 *de novo* patients and 71% of 21 previously operated patients. IGF-I normalization rates of 33% and 53% (for phases 1 and 2 of the present study, respectively) compare with values from other series of 28% (13), 68% (14), 53% (*de novo*) (15), and 76% (previously operated) (15). Eighty percent of our patients had serum IGF-I concentrations less than 300 μg/liter at the end of phase 2 of the study.

Importantly, it is also clear that the pretreatment serum GH level is an important predictor of biochemical success after primary Oct therapy (Fig. 1 and Table 2). Patients with the highest pretreatment GH levels, generally associated with the largest tumors, had the highest GH levels at the end of phase 1. Furthermore, five of the six patients whose serum IGF-I levels remained above 500 μg/liter had pretreatment GH levels greater than 50 mU/liter (Fig. 1).

Overall success rates

None of the previous reports of patients with *de novo* acromegaly treated with primary medical therapy contain a detailed analysis of overall success rates for individual patients.

Table 5 contains these data for our series of patients. Using

TABLE 5. Overall success rates after phases 1 and 2 of UK POTS

Variable	At 24 wk	At 48 wk	Latest observation carried forward[a]
GH <5 mU/liter (<2 μg/liter)	9/24 (38%)	11/14 (79%)	13/24 (54%)
Normal IGF-I	8/24 (33%)	8/15 (53%)	10/24 (42%)
>30% Tumor shrinkage	18/27 (67%)	11/15 (73%)	19/27 (70%)
GH <5 mU/liter and normal IGF-I	4/24 (17%)	7/14 (50%)	8/24 (33%)
GH <5 mU/liter and normal IGF-I and >30% shrinkage	2/24 (8%)	4/14 (29%)	5/24 (21%)

[a] Data combined from patients who withdrew at 24 wk and those who completed both phases of the study.

stringent criteria (*i.e.* serum GH <5 mU/liter, normal IGF-I, and tumor regression of >30%), overall success was achieved in 8% of patients at the end of phase 1, rising to 29% at the end of phase 2. It should be noted that no patient with a pretreatment GH level higher than 50 mU/liter achieved all three targets (Fig. 1 and Table 2). Latest observation analysis showed comparable success rates, reflecting the fact that patients who completed phase 2 were similar in terms of serum GH concentration and tumor size to patients who withdrew at 24 wk (Table 5).

General pituitary function and Oct tolerability

Recovery of impaired pituitary function after macroprolactinoma shrinkage with dopamine agonists is now well described (17). When the substantial tumor regression of GH-secreting adenomas became evident from the present study, we wondered whether similar improvements might be demonstrable. However, this was not a primary objective of the study, and our analysis was confined to retrospective measurement of cortisol, free T_4, and testosterone in early morning basal serum samples. Although this did not reveal any significant changes, it is possible that prospective dynamic testing might have been a more sensitive indicator of changing anterior pituitary function. Given the considerable shrinkage of some of our larger GH tumors, one would certainly predict improvements in pituitary function similar to those demonstrated for macroprolactinomas.

Both sc and im formulations of Oct were well tolerated, and several patients continued primary medical therapy with Oct-LAR after the trial was completed. The incidence of new biliary abnormalities during Oct therapy was similar to that previously described (20) and was not clinically relevant for any patient during the study.

Current status of medical therapy, surgery, and radiotherapy for acromegaly

Our results indicate that many patients with GH-secreting microadenomas could be treated successfully with primary Oct therapy alone. However, cost-benefit analysis makes this an unattractive approach, given the high surgical cure rate for small tumors. Nevertheless, for selected patients who are unfit for anesthesia or refuse surgery or for those concerned about gonadotropin deficiency after surgery or who have no adenoma demonstrable on MRI, primary somatostatin analog therapy is likely to be very successful. Some microadenomas seem to disappear completely on MRI during long-term Oct treatment (15), which is reminiscent of the resolution of some microprolactinomas during dopamine agonist therapy. Whether long-term somatostatin analog therapy has the potential to cure acromegaly in some patients with microadenomas remains to be established.

Surgical cure rates for patients with large macroadenomas, particularly those with marked cavernous sinus invasion, are much less satisfactory. However, our results support the view that most of these tumors should still be surgically debulked before Oct therapy, particularly if the pretreatment GH level is above 50 mU/liter. Colao *et al*. (15) showed that the GH and IGF-I responses to Oct-LAR of *de novo* and previously operated patients were superimposable, and no tumor in either group increased in size during medical therapy. Setting aside financial considerations, it seems likely that most patients with acromegaly could now avoid pituitary radiotherapy and be treated with postoperative Oct alone, thereby conserving anterior pituitary function.

Our results also demonstrate that over 50% of smaller macroadenomas with pretreatment GH levels less than 50 mU/liter can be treated successfully with primary Oct therapy. However, some of these patients may be cured by surgery, and a reasonable approach would be to use preoperative somatostatin analog therapy for 3–6 months, which may marginally improve surgical outcome (4), and recommence somatostatin analog treatment postoperatively in those with residual GH/IGF-I excess.

The GH receptor antagonist pegvisomant is able to normalize serum IGF-I concentrations in the majority of patients with acromegaly (21), but when used as sole therapy in *de novo* patients it could be associated with long-term tumor enlargement. Combination medical therapy with pegvisomant to normalize IGF-I and Oct to restrain tumor growth merits future research. Similarly, the combination of Oct and the long-acting dopamine agonist cabergoline (22) has not been evaluated prospectively in patients with *de novo* acromegaly.

Thus, there are now several effective and well tolerated medical therapies for acromegaly that, used either singly or in combination, are likely to enable successful medical treatment for many patients. However, unlike the situation for patients with prolactinoma, for whom monotherapy with a dopamine agonist is relatively inexpensive, cost-benefit considerations will continue to influence treatment pathways for patients with acromegaly.

Conclusion

We have shown that primary medical therapy with Oct offers the prospect of near normalization of GH/IGF-I levels together with substantial tumor shrinkage in a significant subset of patients with *de novo* acromegaly. This is most likely to occur in patients with pretreatment GH levels less than 50 mU/liter (20 μg/liter). Although primary Oct therapy is safe and generally well tolerated, its place in the management algorithm for acromegaly has yet to be fully clarified.

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