

CLINICAL REVIEW: A Critical Analysis of Pituitary Tumor Shrinkage during Primary Medical Therapy in Acromegaly

Shlomo Melmed, Richard Sternberg, David Cook, Anne Klibanski, Philippe Chanson, Vivien Bonert, Mary Lee Vance, David Rhew, David Kleinberg, and Ariel Barkan

Department of Medicine, Cedars-Sinai Research Institute, David Geffen School of Medicine, University of California (S.M., V.B.), Los Angeles, California 90048; Zynx Health, Inc. (R.S., D.R.), Los Angeles, California 90024; Department of Medicine, Oregon Health & Science University (D.C.), Portland, Oregon 97205; Department of Medicine, Massachusetts General Hospital (A.K.), Boston, Massachusetts 02114; Department of Endocrinology, Hospital Bicetre (P.C.), Paris, France 94275; Department of Medicine, University of Virginia Health Science Center (M.L.V.), Charlottesville, Virginia 22901; Department of Medicine, New York University Medical Center (D.K.), New York, New York 10010; and Department of Medicine, Veterans Administration Medical Center, University of Michigan (A.B.), Ann Arbor, Michigan 48105

Context: Somatostatin analogs have been successfully used to treat patients with GH-secreting pituitary adenomas because they are safe, effective, and usually well tolerated. The results of studies evaluating acromegaly treatment with the somatostatin receptor ligands (SRLs), octreotide and lanreotide, have supported the use of these agents for primary medical therapy before or as an alternative to traditional interventions of surgery and radiotherapy in selected cases.

Evidence Acquisition: We therefore undertook a systematic literature overview to characterize the results of studies involving primary therapy with somatostatin analogs and their effects on pituitary tumor size. Because most studies in which pituitary tumor shrinkage has been assessed involve uncontrolled, open-label, prospective trials or retrospective case series, the lack of a control arm does not permit pooling of data in a metaanalytic fashion to determine tumor size reduction. Therefore, this systematic review was designed to document and stratify data by study design, summarize therapeutic regimens and patient characteristics, assess the percentage of patients showing changes in tumor size, and calculate the weighted average

effect on size reduction.

Evidence Synthesis: Overall, for patients who experience significant shrinkage, an approximately 50% decrease in pituitary mass is achieved when a somatostatin analog is used exclusively or before surgery or radiotherapy. Fourteen studies ($n = 424$) provided a definition of significant tumor shrinkage, and the results showed that 36.6% (weighted mean percentage) of patients receiving primary SRL therapy for acromegaly experienced a significant reduction in tumor size. The weighted mean percent reduction in tumor size was 19.4% for those studies in which all patients received SRLs and change in tumor size was reported for all patients.

Conclusions: Clinical implications are discussed for patients in whom tumor size control with SRLs is an important objective, typically those who have failed surgery or are being treated with primary medical therapy with large tumors. (*J Clin Endocrinol Metab* 90: 4405–4410, 2005)

SOMATOSTATIN ANALOGS HAVE been successfully used to treat patients with GH-secreting pituitary adenomas because they are safe, effective, and usually well tolerated in the majority of patients (1–15). Although these analogs are approved for use after noncurative pituitary surgery, wider experience has led to recommendations for their primary use in selected patients newly diagnosed with acromegaly. Factors influencing the primary use of somatostatin analogs include low cure rates achieved after surgical resection for pituitary macroadenomas with persistent postoperative GH hypersecretion, especially with cavernous sinus invasion, wide variability in surgical experience and skill, prevalence of perioperative side effects, unacceptable anesthetic risk for some patients, and refusal of surgery.

The results of studies evaluating treatment of acromegaly

with the somatostatin receptor ligands (SRLs), octreotide and lanreotide, have supported the use of these agents for primary medical therapy before or as an alternative to traditional interventions of surgery and radiotherapy in selected cases. The effect of medical therapy on tumor mass is an important consideration. Several clinical trials have reported changes in tumor size associated with various somatostatin analog regimens in treating GH-secreting pituitary tumors. The patient populations in these studies were previously treated, previously untreated, or drawn from both categories. Several researchers, typically in narrative reviews, have summarized the results of trials relating to pituitary tumor shrinkage, either as a result of therapy with somatostatin analog before or after other therapies or, less frequently, when used naively as the primary therapy. However, a comprehensive review of all such studies of tumor size has not been reported.

We therefore undertook a systematic literature overview to update, aggregate, and characterize the results of studies involving primary therapy with somatostatin analogs and their effects on pituitary tumor size. A separate review of

First Published Online April 12, 2005

Abbreviations: MRI, Magnetic resonance imaging; SRL, somatostatin receptor ligand.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

primary therapy using dopamine agonists was also undertaken. Because most studies in which pituitary tumor shrinkage has been assessed typically involve uncontrolled, open-label, prospective trials or retrospective case series, the lack of a control arm does not permit the pooling of data in a metaanalytic fashion to determine tumor size reduction. Therefore, this systematic review was designed to document and stratify data by study design, to summarize therapeutic regimens and patient characteristics, to assess the percentage of patients showing changes in tumor size, and, when possible, to calculate the weighted average effect on size reduction in the treatment groups. Clinical implications are discussed for patients in whom tumor size control is an important objective, typically those who have failed surgery or are being treated with primary medical therapy with large residual tumors.

Materials and Methods

Article identification

The peer-reviewed medical literature was searched to identify clinical trials potentially eligible for systematic review. Trials studying pituitary tumor size as an outcome of somatostatin treatment of acromegaly were identified through March 2004 using online bibliographic PubMed database search strategies and reference lists from selected textbooks and retrieved articles.

Inclusion criteria

To be included in this analysis, studies had to be published in the English language, peer-reviewed medical journals and have any of the following designs: randomized controlled trial; prospective, nonrandomized trial; retrospective study; case report; or case series. The study populations comprised patients with diagnosed acromegaly resulting from GH-secreting pituitary adenomas. To be included, patients must not have been treated previously with either radiotherapy or surgery; however, previous treatment with dopamine agonists or somatostatin analog was not a reason for exclusion.

The therapeutic interventions used in these studies needed to include administration of one or more somatostatin analogs as primary therapy or as therapy before surgery or radiotherapy. The somatostatin analogs

evaluated were octreotide, octreotide long-acting release, lanreotide, or lanreotide sustained release. One of the stated study outcomes required change in pituitary tumor size evaluated by magnetic resonance imaging (MRI) in all or in a majority of patients. Because computed tomography scanning has been shown to be less precise than MRI in measuring the size and mass of pituitary tumors, studies primarily using computed tomography scanning were excluded from analysis.

Results

Article selection

We identified 693 studies that evaluated somatostatin analog treatment for acromegaly. Of these, 15 were found to be eligible for study after applying inclusion and exclusion criteria (1–15) (Fig. 1). Of the 15 studies retained for review, three compared treatment *vs.* placebo or control (study type A), one compared drug 1 *vs.* drug 2 (study type B), two compared drug 1 regimen 1 *vs.* drug 1 regimen 2 (study type C), and nine compared outcomes before and after treatment (study type D; Tables 1-4). No randomized, placebo-controlled trials measuring change in pituitary tumor size after primary therapy with somatostatin analogs were identified. Five studies employed diameter dimensions measured by MRI to assess tumor size change (1, 6, 7, 11, 15), nine studies employed tumor volume calculations (2–6, 8–10, 12, 14), and in one study the measurement method was not described (13).

Tumor size effects

Fourteen studies (n = 424) provided a definition of tumor shrinkage and described the percentage of patients receiving an SRL that demonstrated a significant shrinkage in tumor size (Table 5). The 15th study by Amato *et al.* (2) did not provide a definition of significant tumor size shrinkage. Overall, results from the 14 studies showed that 36.6% of patients receiving primary SRL therapy for acromegaly experienced a significant reduction in tumor size. The definition of significant shrinkage ranged from 10% to more than

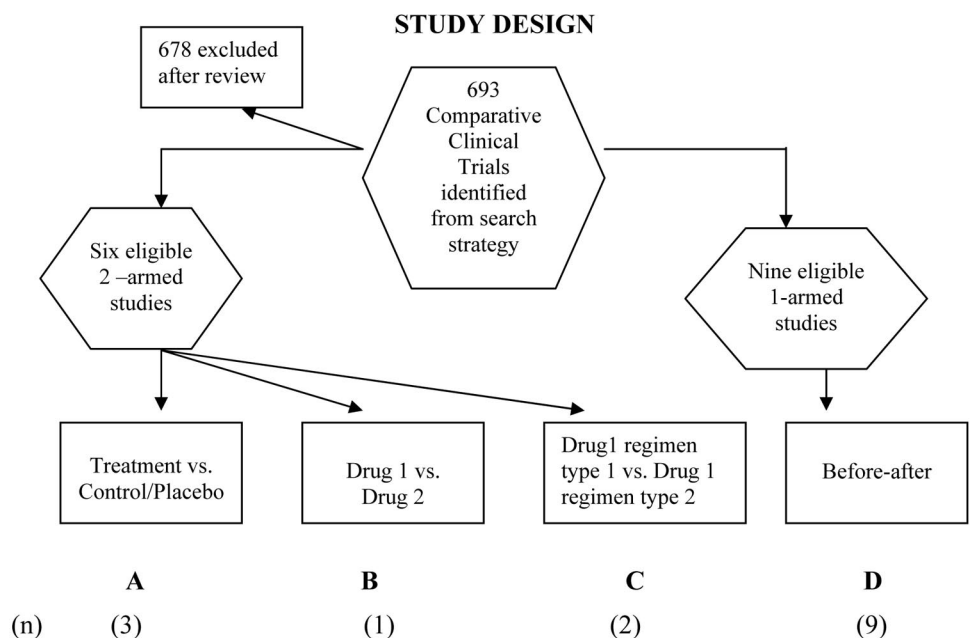


FIG. 1. SRLs: effect on tumor size.

TABLE 1. Study design A (treatment *vs.* control/placebo)

Study	Design	n	Patient data	Treatment
Abe and Ludecke (1)	Retrospective case comparison	90 PT (57 in untreated control group)	45 F (50%), 45 M (50%), 46.1 yr (7–82 yr), 83 MA, 7 mA	Octreotide, minimum daily dose of 300 μ g; minimum duration of 3 months before surgery
Kristof <i>et al.</i> (8)	Prospective open label	11 PT (13 in untreated control group)	4 F (36.3%), 7 M (63.6%), 44.8 yr, 11 MA	Octreotide, 470 \pm 160 μ g, sc, daily for 16.5 \pm 10 wk
Colao <i>et al.</i> (7)	Retrospective case comparison	22 PT (37 in untreated control group)	11 F (50%), 11 M (50%), 40.3 yr (18–62 yr), 21 M, 1 mA	Octreotide LAR, 150–60 μ g daily from 3–6 months

AT, Adjuvant therapy; PT, primary therapy; F, female; LAR, long-acting release; M, male; MA, macroadenoma; mA, microadenoma; N/A, not available, not applicable.

45%. The percentage of patients demonstrating tumor size reduction while receiving short-acting octreotide (37.8%) was not different from that of patients receiving long-acting preparations (34%).

Seven studies ($n = 70$) provided tumor shrinkage data for those patients who responded to treatment and met investigators' various criteria for displaying significant shrinkage (Table 6). The weighted mean percent significant reduction in tumor size for this group of responders was 49.8%. This percentage was calculated by adding the sum of the products for 1) the percent significant shrinkage in each study times, 2) the number of patients responding with significant shrinkage in that study divided by, 3) the total number of patients with significant shrinkage from all seven studies. This percentage was not different between patients who received short-acting octreotide (49.5%) and those who received long-acting preparations (50%).

Three studies ($n = 151$) provided tumor shrinkage data for all study patients receiving an SRL in the study regardless of whether their tumors underwent shrinkage (Table 7). The weighted mean percent reduction in tumor size for this group was 19.4%. The mean percent reduction in tumor size for those patients receiving long-acting preparations was 13.4%.

Specific assumptions were used for calculating the weighted mean percentage of patients with shrinkage and weighted mean percent shrinkages. These assumptions were that heterogeneity of study designs and calculation methods were not to be considered, that all individual percentages were to be used regardless of study criteria for significant shrinkage, and that the midpoint value was to be used when two percentages were provided.

Primary therapy with dopamine agonists

Twenty-six studies were identified that evaluated the effect of dopamine agonist therapy for acromegaly on tumor

size, of which five fulfilled inclusion criteria (16–20). A review of the reference lists of the five retrieved citations suggested the possibility of five additional citations. These were reviewed, and three were excluded because either patients receiving primary therapy were not specifically identified when tumor shrinkage was quantified, or a majority of the tumors studied secreted hormones other than GH. Two additional citations (21, 22) were retained. A review of these seven studies, including primary therapy with dopamine agonists for acromegaly, indicated that tumor shrinkage had been documented in approximately 4–5% of patients.

Discussion

Several studies have reported the efficacy of long-acting somatostatin analogs in achieving biochemical and clinical control of patients with acromegaly either as adjuvant or primary therapy (reviewed in Refs. 23–26). Reports of drug effects on tumor size are limited by a lack of rigor in study design, heterogenous imaging techniques and measurements, and a lack of controls. Nevertheless, except for one study (1), persistent tumor growth has generally not been observed in patients receiving SRL therapy. Furthermore, when somatostatin analogs are discontinued, tumor regrowth appears to occur within 6 months (27). In our review, no randomized, placebo-controlled trials measuring tumor size change after SRL therapy were identified, as a result of which a true metaanalysis could not be performed. However, this critical literature analysis shows that overall, for patients who experience significant shrinkage as variously defined by different investigators, an approximately 50% decrease in pituitary mass is achieved when a somatostatin analog is used exclusively or before surgery or radiotherapy. Absent a random, placebo-controlled trial, a true metaanalysis could not be performed. Importantly, the initial pretreatment tumor size is a determinant of the significance of measured shrinkage. For example, one dimension shrinkage of a

TABLE 2. Study design B (drug 1 *vs.* drug 2)

Study	Design	n	Patient data	Arm 1	Arm 2
Amato <i>et al.</i> (2)	Prospective comparative trial with patients randomized to either of two drugs	23 PT (20 completed trial)	14 F (61%), 9 M (39%), 55 yr (40–72 yr), 10 MA, 10 mA	Lanreotide SR, 30 mg every 10 d, 30 mg every 7 d; duration, 24 months	Octreotide LAR, 20 mg every 28 d, adjusted at 3 months to 30 or 10 mg; duration, 24 months

SR, Sustained release. For other abbreviations, see Table 1.

TABLE 3. Study design C (drug 1 regimen 1 *vs.* drug 1 regimen 2)

Study	Design	n	Patient data	Arm 1	Arm 2
Bevan <i>et al.</i> (5)	Prospective, multicenter, open label	27 PT	10 F (37%), 17 M (63%), 53 yr (21–73 yr), 20 MA, 7 mA	Phase 1, octreotide 100 μ g, sc, 3 times/d (n = 27)	Phase 2, octreotide 20 mg, q im, every 4 wk (n = 15)
Newman <i>et al.</i> (11)	Prospective, comparative, open label, with patients randomized to either of two dosage regimens	26 PT (81 AT)	16 F (61.5%), 10 M (38.5%; 20–78 yr, tumor types not detailed)	Octreotide, 100 <i>vs.</i> 250 μ g, sc, q every 8 h for 6 months	Octreotide, 100 μ g, titrated up to maximum of 1750 μ g daily to improve individual patient response

For abbreviations, see Table 1. The study by Newman *et al.* (11) had an initial phase in which treatment *vs.* placebo was implemented; however, no outcome data from this phase were specified.

10-mm diameter mass to 5 mm (*i.e.* 50%) is clearly of greater clinical significance than a 50% shrinkage of a 4-mm, well-circumscribed, intrasellar microadenoma. In contrast, using a three-dimensional measurement, shrinkage of this mass may be reported as 87%. A limitation inherent in this analysis is lack of independent review of the primary MRI data and reliance on published scan readings.

Clinical benefits of tumor mass shrinkage include relief of vital structure impingement, patient reassurance that the mass is shrinking, and possibly a lowered risk of intratumoral hemorrhage. Surgery is the first-line therapy for well-circumscribed microadenomas, and medical therapy is indicated should surgery not be curative (28, 29). Primary SRL therapy may be offered in selected patients with unaccept-

TABLE 4. Study design D (before-after)

Study	Design	n	Patient data	Arm 1
Attanasio <i>et al.</i> (3)	Prospective, open label	30 PT (62 AT)	All patients, 61 F (66%), 31 M (34%), 50 yrs (20–79 yr), 21 MA, 12 mA, 59 other	Lanreotide, 60 mg, im, every 28 d for 3 months, then individually tailored to achieve mean GH < 2.5 μ g/liter; duration, 6–48 months (mean, 24 months)
Lucas <i>et al.</i> (9)	Prospective, open label	104 PT	62 F (60%), 42 M (40%), 48.2 yr, 78 MA, 18 mA, 8 not described	Lanreotide, 30 mg, im every 10 d for 1, 2, or 3 or more months before transsphenoidal surgery
Colao <i>et al.</i> (6)	Prospective, open label	15 PT (21 AT)	10 F (67%), 5 M (23%), 50.5 yr (24–77 yr), 12 MA, 3 mA	Octreotide LAR, initial dose of 20 mg, im, every 28 d, then increased; duration, 15–24 months
Baldelli <i>et al.</i> (4)	Prospective, open label	23 PT (93 AT)	15 F (65%), 8 M (35%), 49.4 yr (22–77 yr), 15 MA, 8 mA	Lanreotide, 30 mg q im, every 14 d for 3 months; then change in interval based on GH levels; duration, 6–24 months
Tachibana <i>et al.</i> (14)	Retrospective, case series	3 PT	2 F (67%), 1 M (33%), 35 yr (30–45 yr), 3 MA	Octreotide, 100 μ g, sc, every 2 wk
Tamura <i>et al.</i> (15)	Prospective, open label	9 PT	4 F (44%), 5 M (56%), 43 yr (32–55 yr), 6 MA, 3 mA	Octreotide, 120–240 μ g daily, continuous infusion for 2–4 wk
Lundin <i>et al.</i> (10)	Prospective, open label	17 PT	12 F (70.5%), 5 M (29.5%), 51 yr, 13 MA, 4 mA	Octreotide, 300 μ g sc daily (median dose); duration, 9–70 months
Stevensaert and Beckers (13)	Prospective, open label	64 PT	Not cited	Octreotide group 1 (n = 14): 100 μ g, 3 times/d for 3–6 wk before surgery; group 2 (n = 50), 3–9 months, 13–39 months; dose increased to 500 μ g, 3 times/d (n = 18)
Plockinger <i>et al.</i> (12)	Prospective, open label	10 PT	6 F (60%), 4 M (40%), 42.3 yr (26–67 yr), 10 MA	Octreotide, sc, increased from 100 μ g to 1500 μ g/d for 3–6 months

For abbreviations, see Table 1.

TABLE 5. Percentage of patients with significant tumor shrinkage

Study	Arm	Total no. of PT patients enrolled in study	Criterion for significant shrinkage (%)	% of patients with significant shrinkage (no./total)
Attanasio <i>et al.</i> (3)	Lanreotide, 60 mg	30 (22 assessed)	>25	50 (11/22)
Lucas <i>et al.</i> (9)	Lanreotide, 30 mg	104	>20	29 (31/104)
Bevan <i>et al.</i> (5)	Octreotide	27	>30	73 (20/27)
Colao <i>et al.</i> (6)	Octreotide LAR	15	Moderate to notable +	60 (9/15)
Abe and Ludecke (1)	Octreotide	90	>2 mm in diameter	31 (28/90)
Baldelli <i>et al.</i> (4)	Lanreotide, 30 mg	23	≥20	23 (5/23)
Tachibana <i>et al.</i> (14)	Octreotide	3	>45	67 (2/3)
Kristof <i>et al.</i> (8)	Octreotide	11	>25	36 (4/11)
Newman <i>et al.</i> (11)	Octreotide	26 (13 assessed)	≥10	46 (6/13)
Tamura <i>et al.</i> (15)	Octreotide	9	>20	67 (6/9)
Colao <i>et al.</i> (7)	Octreotide	22	>30	23 (5/22)
Lundin <i>et al.</i> (10)	Octreotide	11	>25	73 (8/11)
Stevensaert and Beckers (13)	Octreotide	64	>25	23 (15/64)
Plockinger <i>et al.</i> (12)	Octreotide	10	>20	50 (5/10)

Fourteen studies; number of assessed patients, 424; number of patients with significant shrinkage, 155; percentage with significant shrinkage, 155/424 (36.6%); percentage of patients with significant shrinkage, 36.6%. Assumptions for calculating the percentage of patients with significant tumor shrinkage: heterogeneity of study designs and calculation methods is not considered. All individual percentages are used regardless of study criteria for significant shrinkage. See Table 1 for abbreviations.

TABLE 6. Weighted mean percent significant shrinkage in tumor size

Study	Arm	Total no. of patients	Study criterion for significant shrinkage (%)	No. of patients responding with significant shrinkage	Mean [or median (%)] % significant shrinkage in volume
Lucas <i>et al.</i> (9)	Lanreotide, 30 mg	104	>20	30	42.2 (20.4–77)
Bevan <i>et al.</i> (5)	Phase 2, octreotide LAR	15	>30	12	67
Colao <i>et al.</i> (6)	Octreotide LAR	15	Moderate to notable	9	53 (18–100)
Tachibana <i>et al.</i> (14)	Octreotide	3	>40	2	50
Kristof <i>et al.</i> (8)	Octreotide	11	>25	4	38.5 (29–48)
Lundin <i>et al.</i> (10)	Octreotide	17 (11 assessed)	>18	8	51 (26–67)
Plockinger <i>et al.</i> (12)	Octreotide	9	>20	5	55.5 (26–85)
Seven studies		168		70	

Weighted mean percent significant shrinkage in tumor size, 49.8%. Assumptions for calculating weighted mean percent significant shrinkage in tumor size, heterogeneity of study designs and calculation methods is not considered. Percentages presented as medians (two studies) are included with means (five studies) to calculate the weighted mean. See Table 1 for abbreviations.

able anesthetic risk, cardiovascular or pulmonary complications, (30), and macroadenomas not impinging on the optic chiasm, with little likelihood of surgical cure. Because the majority of patients with macroadenomas, especially those with tumors extending into the cavernous sinus, will not be cured surgically, postoperative therapy is required in most patients. For those patients with persistent GH hypersecretion and visible tumor on MRI, which suggests the probability of cure, reoperation by an experienced pituitary surgeon after initial surgery by an inexperienced surgeon is recommended (31). No controlled prospective data are currently available on the value of noncurative debulking surgery. Medical therapy options include the use of dopamine agonists, SRL therapy, and pegvisomant (32). Overall, only

a small percentage of patients, usually those with only minimal IGF-I elevations, will be controlled by dopamine agonists. For patients with significant residual tumor mass in whom tumor control is clinically indicated and for whom repeat surgery is not an efficacious option, SRL therapy is indicated. Because the overall maximal efficacy of SRL therapy is approximately 70%, a significant minority of patients can be expected to have persistent hormone hypersecretion. If control is inadequately achieved with maximal SRL doses and added dopamine agonists, or if patients are intolerant of SRLs, therapy should be initiated with pegvisomant, the GH receptor antagonist, sometimes in the setting of radiation therapy (33). The advantage of SRL is tumor control; the advantage of pegvisomant is near 100% IGF-I normalization.

TABLE 7. Weighted mean percent shrinkage in tumor size for all patients receiving SRLs in a study

Study	Arm	Total no. of patients enrolled in study	Median [or mean (%)] shrinkage in volume calculated for all patients enrolled in study
Lucas <i>et al.</i> (9)	Lanreotide, 30 mg	104	10
Bevan <i>et al.</i> (5)	Phase 1, octreotide	27	20 MA, 43%; 7 mA, 49%
Amato <i>et al.</i> (2)	Lanreotide, 30 mg	10	30%
Amato <i>et al.</i> (2)	Octreotide LAR	10	34.8
Three studies		151	

Weighted mean percent shrinkage in tumor size when calculated for all patients enrolled in a study, 19.4%. Assumptions for calculating weighted mean percent shrinkage when reported for all enrolled patients in a study; heterogeneity of study designs and calculation methods is not considered. Midpoint value is selected when two percentages are provided. Percentages presented as medians (two studies) are included with means (one study) to calculate the weighted mean. See Table 1 for abbreviations.

In patients who have failed both surgical and optimal medical therapy or who have evidence of continued tumor growth while receiving medical therapy, radiotherapy should be considered depending on clinical disease activity and the degree or persistence of biochemical disease.

Because potential adverse effects limit the efficacy of treatments for acromegaly, integrated treatment decisions are best made by a team that includes endocrinologists and surgeons. Long-term treatment cost is also a significant determinant of therapeutic choice. The ultimate choice of therapy should be based upon an informed patient understanding of the potential disadvantages of therapeutic approaches *vs.* their effectiveness in managing a complex metabolic disorder by reducing its comorbidities and by ultimately achieving favorable mortality outcomes (34, 35).

Acknowledgments

Received December 15, 2004. Accepted April 5, 2005.

Address all correspondence and requests for reprints to: Dr. Shlomo Melmed, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, California 90048. E-mail: melmed@csmc.edu.

No commercial support from any proprietary organization was used for this study.

References

- Abe T, Ludecke DK 2001 Effects of preoperative octreotide treatment on different subtypes of 90 GH-secreting pituitary adenomas and outcome in one surgical centre. *Eur J Endocrinol* 145:137–145
- Amato G, Mazziotti G, Rotondi M, Iorio S, Doga M, Sorvillo F, Manganello G, Di Salle F, Giustina A, Carella C 2002 Long-term effects of lanreotide SR and octreotide LAR on tumour shrinkage and GH hypersecretion in patients with previously untreated acromegaly. *Clin Endocrinol (Oxf)* 56:65–71
- Attanasio R, Baldelli R, Pivonello R, Grottoli S, Bocca L, Gasco V, Giusti M, Tamburrano G, Colao A, Cozzi R 2003 Lanreotide 60 mg, a new long-acting formulation: effectiveness in the chronic treatment of acromegaly. *J Clin Endocrinol Metab* 88:5258–5265
- Baldelli R, Colao A, Razzore P, Jaffrain-Rea ML, Marzullo P, Ciccarelli E, Ferretti E, Ferone D, Gaia D, Camanni F, Lombardi G, Tamburrano G 2000 Two-year follow-up of acromegalic patients treated with slow release Lanreotide (30 mg). *J Clin Endocrinol Metab* 85:4099–4103
- Bevan J, Atkin S, Atkinson AB, Bouloux PM, Hanna F, Harris PE, James RA, McConnell M, Roberts GA, Scanlon MF, Stewart PM, Teasdale E, Turner HE, Wass JA, Wardlaw JM 2002 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. *J Clin Endocrinol Metab* 87:4554–4563
- Colao A, Ferone D, Marzullo P, Cappabianca P, Cirillo S, Boerlin V, Lanranjan I, Lombardi G 2001 Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. *J Clin Endocrinol Metab* 86:2779–2786
- Colao A, Ferone D, Cappabianca P, del Basso De Caro ML, Marzullo P, Monticelli A, Alfieri A, Merola B, Cali A, de Divitiis E, Lombardi G 1997 Effect of octreotide pretreatment on surgical outcome in acromegaly. *J Clin Endocrinol Metab* 82:3308–3314
- Kristof R, Stoffel-Wagner B, Klingmuller D, Schramm J 1999 Does octreotide treatment improve the surgical results of macro-adenomas in acromegaly? A randomized study. *Acta Neurochir* 141:399–405
- Lucas T, Astorga R, Catala M, Spanish Multicenter Lanreotide Study Group on Acromegaly 2003 Preoperative Lanreotide treatment for GH-secreting pituitary adenomas: effect on tumour volume and predictive factors of significant tumour shrinkage. *Clin Endocrinol (Oxf)* 58:471–481
- Lundin P, Engstrom B, Karlsson F, Burman P 1997 Long-term octreotide therapy in growth hormone-secreting pituitary adenomas: evaluation with serial MR. *AJNR Am J Neuroradiol* 18:765–772
- Newman C, Melmed S, George A, Torigian D, Duhany M, Snyder P, Young W, Klibanski A, Molitch ME, Gagel R, Sheeler L, Cook D, Malarkey W, Jackson I, Vance ML, Barkan A, Frohman L, Kleinberg DL 1998 Octreotide as primary therapy for acromegaly. *J Clin Endocrinol Metab* 83:3034–3040
- Plockinger U, Reichel M, Fett U, Saeger W, Quabbe H 1994 Preoperative octreotide treatment of growth hormone-secreting and clinically nonfunctioning pituitary macroadenomas: effect on tumor volume and lack of correlation with immunohistochemistry and somatostatin receptor scintigraphy. *J Clin Endocrinol Metab* 79:1416–1423
- Stevens A, Beckers A 1996 Presurgical octreotide: treatment in acromegaly. *Metabolism* 45(Suppl 1):72–74
- Tachibana E, Saito K, Yoshida J 1999 Preoperative short-term administration of octreotide for facilitating transsphenoidal removal of invasive growth hormone-secreting macroadenomas. *Neurol Med Chir* 39:496–501
- Tamura M, Yokoyama N, Abe Y, Sera N, Tominaga T, Ashizawa K, Ejima E, Kiriya T, Uetani M, Kuwayama A, Nagataki S 1998 Preoperative treatment of growth hormone-producing pituitary adenoma with continuous subcutaneous infusion of octreotide. *Endocr J* 45:269–275
- Abs R, Verhelst J, Maiter D, Van Acker K, Nobels F, Coolens JL, Mahler C, Beckers A 1998 Cabergoline in the treatment of acromegaly: a study in 64 patients. *J Clin Endocrinol Metab* 83:374–378
- Cozzi R, Attanasio R, Barausse M, Dallabonzana D, Orlandi P, Da Re N, Branca V, Oppizzi G, Gelli D 1998 Cabergoline in acromegaly: a renewed role for dopamine agonist treatment? *Eur J Endocrinol* 139:516–521
- Halse J, Harris AG, Kvistborg A, Kjartansson O, Hansen E, Smiseth O, Djosland O, Haas G, Jervell J 1990 A randomized study of SMS 201–995 versus bromocriptine treatment in acromegaly: clinical and biochemical effects. *J Clin Endocrinol Metab* 70:1254–1261
- Plockinger U, Quabbe HJ 1991 Evaluation of a repeatable depot-bromocriptine preparation (Parlodel LAR) for the treatment of acromegaly. *J Endocrinol Invest* 14:943–948
- Sachdev Y, Gomez-Pan A, Tunbridge WM 1975 Bromocriptine therapy in acromegaly. *Lancet* 2:1164–1168
- Oppizzi G, Liuzzi G, Chioldini P, Dallabonzana D, Spelta B, Silvestrini F, Borghi G, Tonon C 1984 Dopaminergic treatment of acromegaly: different effects on hormone secretion and tumor size. *J Clin Endocrinol Metab* 58:988–992
- Colao A, Ferone D, Marzullo P, DiSarno A, Cerbone G, Sarnacchiaro F, Cirillo S, Merola B, Lombardi G 1997 Effect of different dopaminergic agents in the treatment of acromegaly. *J Clin Endocrinol Metab* 82:518–523
- Freda PU 2002 Somatostatin analogs in acromegaly. *J Clin Endocrinol Metab* 87:3013–3018
- Lamberts SW, van der Lely AJ, de Herder WW, Hofland LJ 1996 Octreotide. *N Engl J Med* 25:246–254
- Hofland LJ, Lamberts SW 2003 The pathophysiological consequences of somatostatin receptor internalization and resistance. *Endocr Rev* 24:28–47
- Ben-Shlomo A, Melmed S 2003 Clinical review 154: the role of pharmacotherapy in perioperative management of patients with acromegaly. *J Clin Endocrinol Metab* 88:963–968
- Ezzat S, Snyder PJ, Young WF, Boyay LD, Newman C, Klibanski A, Molitch ME, Boyd AE, Sheeler L, Cook DM 1992 Octreotide treatment of acromegaly. A randomized, multicenter study. *Ann Intern Med* 117:711–718
- Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, Ho, Kleinberg D, Lamberts S, Laws E, Lombardi G, Vance ML, Werder KV, Wass J, Giustina A 2002 Acromegaly treatment consensus workshop participants. Guidelines for acromegaly management. *J Clin Endocrinol Metab* 87:4054–4058
- Clemmons DR, Chihara K, Freda PU, Ho KK, Klibanski A, Melmed S, Shalet SM, Strasburger CJ, Trainer PJ, Thorner MO 2003 Optimizing control of acromegaly: integrating a growth hormone receptor antagonist into the treatment algorithm. *J Clin Endocrinol Metab* 88:4759–4767
- Giustina A, Boni E, Romanelli G, Grassi V, Giustina G 1995 Cardiopulmonary performance during exercise in acromegaly, and the effects of acute suppression of growth hormone hypersecretion with octreotide. *Am J Cardiol* 75:1042–1047
- Barker II FG, Klibanski A, Swearingen B 2003 Transsphenoidal surgery for pituitary tumors in the United States, 1996–2000: mortality, morbidity, and the effects of hospital and surgeon volume. *J Clin Endocrinol Metab* 88:4709–4719
- Laws ER, Sheehan JP, Sheehan JM, Jagnathan J, Jane Jr JA, Oskouian R 2004 Stereotactic radiosurgery for pituitary adenomas: a review of the literature. *J Neurooncol* 69:257–272
- Van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klibanski A, Herman-Bonert V, Melmed S, Vance ML, Freda PU, Stewart PM, Friedn KE, Clemmons DR, Johannsson G, Stavrou S, Cook DM, Phillips LA, Strasburger CJ, Hackett S, Zib KA, Davis RJ, Scarlett JA, Thorner MO 2001 Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 358:1754–1759
- Holdaway IM, Rajasoorya RC, Gamble GD 2004 Factors influencing mortality in acromegaly. *J Clin Endocrinol Metab* 89:667–674
- Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM, Bates AS 2004 Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. *J Clin Endocrinol Metab* 89:1613–1617