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Somatostatin Analogs as Primary Medical Therapy for Acromegaly

Ann Danoff[1] and David Kleinberg[2]

[1]New York University School of Medicine, Section Chief, Endocrinology, Harbor Health Care (Manhattan) VA, New York, NY; and [2]New York University School of Medicine, New York, NY

Acromegaly is a debilitating disease usually caused by a growth-hormone secreting pituitary adenoma. Therapeutic goals include improvement of symptoms, reduction in tumor mass, biochemical normalization, and preservation of pituitary function. Treatment options include transsphenoidal surgery, radiation, and pharmacotherapy. In view of the good cure rate, surgery remains the therapeutic modality of choice for most patients with microadenomas or well-circumscribed macroadenomas. In contrast, >40% of patients with invasive macroadenomas (who make up the majority of patients with acromegaly) will have residual disease following surgery, and require additional therapeutic intervention. Somatostatin analogs result in biochemical normalization in >60% of non-operated patients, and are well tolerated. Therefore, somatostatin analogs have emerged as a rational first-line treatment for the appropriately selected patient with acromegaly.

Key Words: Acromegaly; growth hormone; somatostatin analog; octreotide; lanreotide.

Introduction

Acromegaly is a rare, debilitating disease with an insidious onset, usually caused by a growth hormone (GH)–secreting pituitary adenoma. When inadequately treated, the disease is associated with decreased life expectancy *(1–4)*, as well as serious systemic disorders such as heart and lung disease *(5–7)*. Therapeutic goals include amelioration of the signs and symptoms of the disease, reduction of tumor mass, preservation of pituitary function, and normalization of biochemical abnormalities *(8,9)*. Outcome studies demonstrate improvement in survival as well as less morbidity when GH is reduced to <2.5 ng/mL, and insulin-like growth factor-1 (IGF-1) levels are normalized *(10–13)*. Treatment options for acromegaly include transsphenoidal surgery *(12–19)*, radiation *(20,21)*, and pharmacotherapy *(22–25)*. Before the introduction of somatostatin analogs, there was limited success in achieving biochemical cure. Even in the hands of experienced surgeons, pituitary surgery fails to cure 50–60% of people with macroadenomas (present in the majority of people with acromegaly), conventional radiotherapy takes >10 yr to achieve GH < 5 ng/mL, and dopaminergic agonists normalize IGF-1 levels in only 10% of patients. By contrast, a single depot injection of the long-acting somatostatin analog, octreotide, can reduce GH to <5 ng/mL in 97% of patients, to <2.5 ng/mL in ~66% of patients, and normalizes IGF-1 in ~67% of patients *(26)*. The observation that somatostatin analogs successfully achieve long-term biochemical cure when used as secondary or adjunctive therapy, or in patients not treated with other modalities because of medical contraindications or personal preferences, led to investigation of the use of somatostatin analogs as primary therapy for acromegaly *(24,27–39)*. Somatostatin analogs have emerged as important agents that, in the appropriately selected patient, may be successfully employed as primary therapy.

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Author to whom all correspondence and reprint requests should be addressed: Ann Danoff, New York University School of Medicine, Section Chief, Endocrinology, Harbor Health Care (Manhattan) VA, 423 E. 23rd Street, New York, NY 10010. E-mail: danoffann@aol.com

Background

Somatostatin (somatotropin release–inhibiting factor [SRIF]), was originally isolated in the 1970s as a hypothalamic GH-release inhibitory peptide *(40)*. There are two biologically active native peptides—SRIF-14, and the aminoterminally extended form, SRIF-28—encoded on chromosome 3 *(41)* and synthesized as part of a larger precursor, prepro-SRIF *(42)*. The precursor undergoes proteolytic cleavage by prohormone convertases to release the mature peptides *(43)*. SRIF is a widely distributed peptide, found in peripheral tissues and the central nervous system. Among its diverse biologic effects, SRIF inhibits the secretion of GH and thyroid-stimulating hormone from the anterior pituitary, and insulin, gastrin, and glucagon release from the pancreas *(44–46)*.

Somatostatin exerts its biologic effects through one of five somatostatin receptors (SSTR1–5) *(46–48)*, each of which is encoded on a separate chromosome. These SSTRs belong to the superfamily of seven-transmembrane-spanning domain G protein–coupled membrane receptors and utilize a variety of signal-transduction pathways *(49,50)*. SSTR2 and 5 are the predominant subtypes expressed in

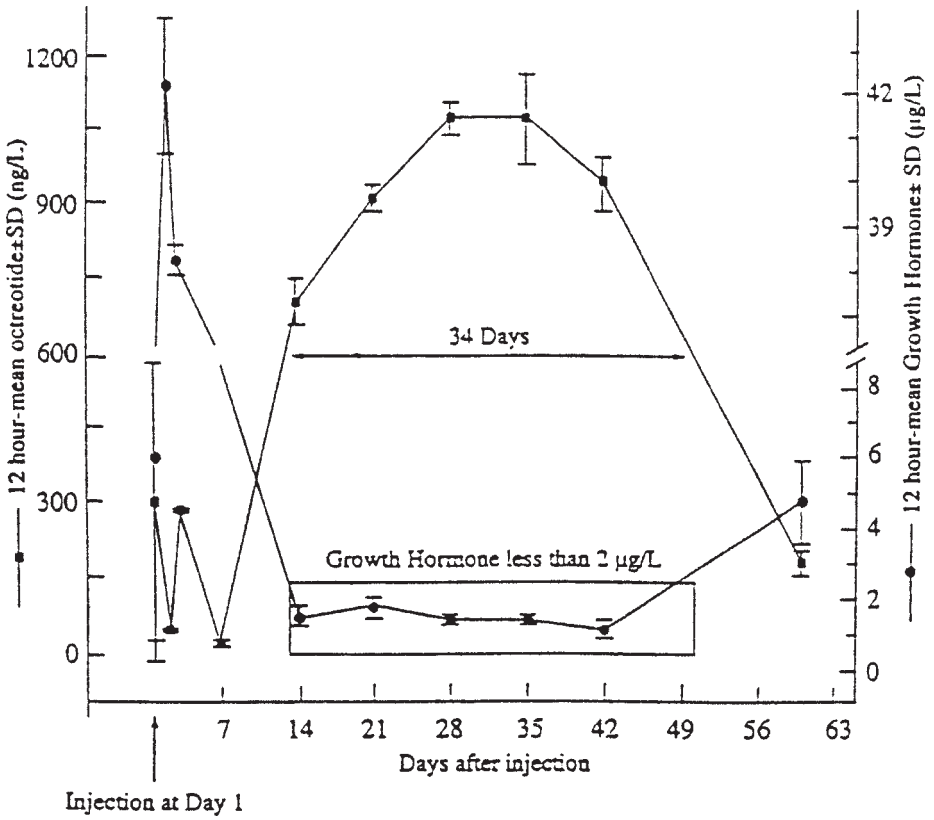

Fig. 1. GH response following single injection of octreotide LAR.

the normal pituitary *(51)*, and in general somatotropin adenomas recapitulate this expression pattern *(52–56)*.

Naturally occurring SRIF-14 and SRIF-28 bind to all five human SSTR subtypes with high affinity. Therapeutic use of these peptides is limited by their rapid proteolytic degradation ($t_{1/2}$ < 3 min), resulting in the need for frequent sc injection, or, alternatively, continuous infusion. Further, therapeutic use of the native peptides does not exploit the tissue-specific expression of SSTR subtypes on neoplastic tissue. To maximize therapeutic efficacy, and improve the side effect profile, several synthetic SRIF analogs have been developed.

Available Somatostatin Analogs

Octreotide (D-Phe-Cys-Phe-D-Trp-Lys-Thr-OH, Sandostatin; Sandoz Pharma), the first SRIF analog that became available for use in the mid-1980s, established the clinical importance of somatostatin analogs *(57)*. It is an octapeptide with an in vivo half-life of 2 h, binds with highest affinity to SSTR2, and less avidly to SSTR5. Octreotide inhibits GH secretion with a 45-fold greater potency than native SRIF, while inhibiting insulin release only 1.3-fold compared to the native peptide *(27,58)*. A single sc injection suppresses GH secretion for up to 5 h *(26,59)*. In a double-blind, placebo-controlled trial, octreotide (8-h injections) significantly attenuated GH and IGF-1 levels in >90% of patients *(59–62)*. In one study *(63)*, mean serum GH fell from 30.9 to 5.7 µg/L, and serum IGF-1 was normalized in >50% of visits in 64% of patients. Efficacy of octreotide action is dependent upon frequency of drug administration, total daily dose, tumor size, and pretreatment GH levels *(59)*. Increasing the frequency of administration suppresses GH levels more effectively, and continuous sc infusion (up to 600 µg/d) provides sustained GH control. Total daily doses of between 300 and 750 µg are generally employed; further increases in dose are usually not beneficial *(25)*.

To enhance convenience and improve compliance, several long-acting somatostatin analog formulations have been developed, including octreotide LAR, lanreotide, and lanreotide autogel. By complexing octreotide with a biodegradable glucose polymer, octreotide LAR was generated *(28, 63)*. Initiation of octreotide LAR therapy is associated with a transient increase in GH, followed by a gradual decline that reaches its nadir by 14 d *[28]*; Fig. 1). The medication has an extended duration of action, and its effect is comparable to octreotide when administered once every 28 d by im injection.

Lanreotide (Dnal-cys-tyr-Dtrp-lys-val-cys-thr, Somatuline; Ipsen Biotech), another long-acting octapeptide somatostatin analog currently available in Europe, is prepared in microspheres of biodegradable lactide/glycolide copolymers and is administered by im injection every 7–14 d *(64)*. GH

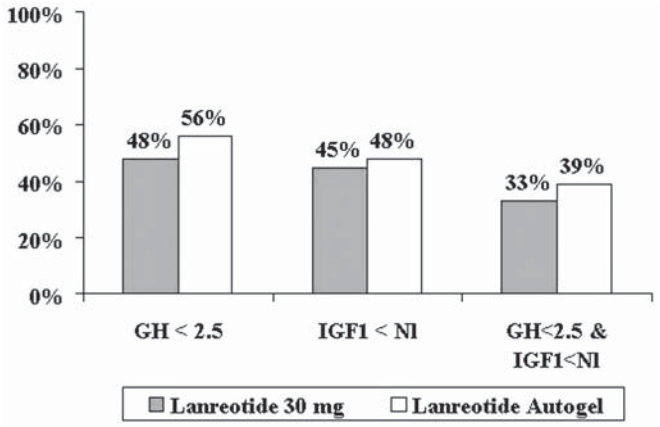

Fig. 2. Percentage of responders to lanreotide and lanreotide autogel.

Table 1
Comparison of Somatostatin Analogs

Analog	Drug	Dose	Formulation
Octreotide	Sandostatin	100 mg subcutaneously, three times daily	
Octreotide LAR	Sandostatin LAR	30 mg intramuscularly, every 28 d	Biodegradable glucose polymer
Lanreotide	Somatuline	30 mg intramuscularly, every 10–14 d	Lactide/glycolide copolymers
Lanreotide autogel	Autogel	60 mg deep subcutaneously, every 28 d	Pure aqueous solution
SOM 230		NA[a]	NA[a]

[a]NA, not available.

fell from a mean of 14.1 to 6.4 ng/mL, and IGF-1 normalized in 61% of patients with acromegaly treated with lanreotide. GH and IGF-1 response to lanreotide autogel, a pure aqueous solution of lanreotide that can be self-administered by deep sc injection every 28 d, has similar efficacy (Fig. 2) *(65)*.

Not yet available for clinical use is another somatostatin analog, SOM 230 (Novartis). It is a cyclohexapeptide with unique antisecretory properties in vitro and in animal models *(66)*. SOM 230 binds to all the SSTRs (except subtype 4) and has a 40-fold higher affinity for SSTR5 than octreotide. SOM 230 is threefold more potent than octreotide in inhibiting GH secretion from cultured rat pituitary cells. It effectively lowers GH in rhesus and cynomolgous monkeys and rats, while having little effect on basal insulin and glucagon secretion or glycemic control. Interestingly, when delivered by osmotic pump to rats, SOM 230 lowered IGF-1 far more effectively than octreotide at comparable GH-lowering efficacy, perhaps by interfering with both GH-dependent and GH-independent IGF-1 secretion. Because of this favorable metabolic profile, coupled with a (relatively) long half-life of 23 h, this novel peptide is currently in phase 2 trials. Table 1 summarizes available somatostatin analogs.

Efficacy of Somatostatin Analogs on GH and IGF-1 When Used as Primary Therapy

Many trials have confirmed the efficacy of somatostatin analogs when used as secondary or adjunctive therapy *(28–36)*. Interest in the use of these agents as primary therapy arose from the reduction of GH and IGF-1 levels that was observed among the small number of previously untreated patients who were included in studies in which they were administered somatostatin analogs preoperatively *(29,33, 66–69)*. One prospective, nonrandomized multicenter study designed specifically to address the efficacy of somatostatin analogs as primary therapy (in 27 patients) was recently published *(39)*. Two earlier nonrandomized studies *(37,38)* include data on a relatively large number of patients, comparing 26 and 15 previously untreated patients with 81 and 21 patients who had received prior therapy, respectively. Several of the important questions that these studies address are summarized next, and may modify our approach to patients with acromegaly.

Does Treatment with Somatostatin Analogs Result in Clinical Improvement?

Improvement in the overall signs and symptoms associated with acromegaly has been documented in patients receiving short-acting or longer-acting somatostatin analogs and was equally effective when used as primary or secondary therapy. For example, in one series *(37)*, symptoms such as increased perspiration, fatigue, and joint pain improved in 50–100% of the primary treatment group, and 62–88% of the secondary treatment group during 3 yr of octreotide therapy. Headache also improved *(37)*, but this was one instance in which short-acting somatostatin analogs were more effective than longer-acting ones *(71)*. Responses observed by several groups are summarized in Table 2.

Are Somatostatin Analogs Effective in Achieving a Biochemical Cure in Previously Untreated Patients?

Using similar criteria (see footnote to Table 3), primary therapy with somatostatin analogs resulted in improvement of GH in 43, 73.3, and 79% and normalized IGF-1 in 68, 53.3, and 53% of patients in studies by Newman et al. *(37)*, Colao et al. *(38)*, and Bevan et al. *(39)*, respectively. These disease-control rates were comparable with those achieved in patients in whom analog therapy was employed as secondary or adjunctive therapy, with GH and IGF-1 normalized in 22 and 62%, respectively, in previously treated patients reported by Newman et al. *(37)* and in 76.2 and 71.4% of those reported by Colao et al. *(38)*.

Table 2
Symptomatic Improvement in Patients Treated with Somatostatin Analogs as Primary (1º) or Secondary (2º) Therapy[a]

Study	Therapy	Headache	Fatigue	Sweating	Arthralgias	Carpal tunnel syndrome	Snoring
Newman et al. *(37)*	1º	+ (60%)	+ (71%)	+ (67%)	+ (75%)	NA	NA
Newman et al. *(37)*	2º	+ (72%)	+ (65%)	+ (75%)	+ (63%)		
Colao et al. *(38)*	1º	+	+	+	+		
Colao et al. *(38)*	2º	+	+	+	+		
Bevan et al. *(39)*	1º	*	+	+	*	+	+

[a] *= Not prominent at baseline; + = improved; NA = not available.

Table 3
Biochemical and Radiologic Improvement in Patients Treated with Somatostatin Analogs as Primary (1º) or Secondary (2º) Therapy[a]

Study/therapy	*n*	GH improvement (%)	IGF-1 improvement	Tumor regression	Tumor regression >25% (vol)
Newman et al. *(37)*, 1º	26	43	68%	13/26 (50%)	3/13 (23%)
Newman et al. *(37)*, 2º	81	22	62%		NA
Colao et al. *(38)*, 1º	15	73.3	53.3%	12/15 (80%)	12/15 (80%)
Colao et al. *(38)*, 2º	21	76.2	71.4%	5/9 (55%)	NA
Bevan et al. *(39)*, 1º	27	79	8/15 (53%)	27/27 (100%)	20/23 (73%)

[a] Definitions of GH and IGF-1 improvement are as in (a) Newman et al. *(36)*, (b) Colao et al. *(37)*, and (c) Bevan et al. *(38)*:

(a) GH by radioimmunoassay (RIA) (Nichols) ≤2 μg/L during at least four study visits; unextracted IGF-1 by RIA (Nichols) reduced into normal range for age-matched controls during at least half of study visits.

(b) Basal GH <2.5 μg/L (HGH-CTK-IRMA; Sorin); ethanol-extracted IGF-1 by immunoradiometric assay (IRMA) (Diagnostic Systems), normalized for age.

(c) GH <2 μg/L by chemiluminescent IRMA (Nichols); IGF-1 by IRMA (Nichols) normalized for age and gender.

Can Somatostatin Analogs Achieve Clinically Significant Tumor Regression or Restrain Further Growth?

For a treatment to be clinically effective as primary therapy, it must prevent further tumor growth in a significant number of patients and, optimally, induce tumor regression. It is important to note that tumor expansion was found to be extremely rare in patients being treated with somatostatin analogs *(24,37–39)*, although some differences with respect to the extent of tumor regression were observed. Following initial decrease in tumor volume, only one patient exhibited modest tumor reexpansion with long-term treatment, albeit not back to pretreatment size *(39)*. In contrast to the tumor regression noted in ~50% of the *de novo* patients reported by Newman et al. *(37)*, a decrease in tumor size occurred in 80 and 100% of the *de novo* patients reported by Colao et al. *(38)* and Bevan et al. *(39)*, respectively. Tumor volume was decreased by >25% to 30% in <25% of the patients reported by Newman et al. *(37)*, but was reported in 80 and 73% of patients reported by Colao et al. *(38)* and Bevan et al. *(39)*, respectively. These differences may result from use of different techniques to assess tumor volume (including retrospective analysis of magnetic resonance imaging scans in the study by Newman et al. *[37]*), which probably resulted in an underestimate of achievable tumor regression. Microadenomas completely disappeared in two of three, and two of seven patients included in the series by Colao et al. *(38)* and Bevan et al. *(39)*, respectively. Overall, five of seven microadenomas decreased by over 60% in Bevan et al.'s *(39)* series, but the tumor volume decreased by only 18% in the third patient with a microadenoma included in Colao et al.'s *(38)* series, indicating variable and unpredictable individual responsiveness.

The impact on GH, IGF-1, and tumor regression in *de novo* (primary) and secondary treatment groups from the three large studies reviewed above is summarized in Table 3.

Is Biochemical Response and/or Tumor Regression Predictable from Data Available at Presentation? Is There a Correlation Between Biochemical and Radiologic Responsiveness?

Median pretreatment GH and IGF-1 levels were higher in patients with macroadenomas than microadenomas (44.8 vs 13.8 mU/L, and 718 vs 532 μg/L, respectively) in the patients reported by Bevan et al. *(39)*, although there was significant overlap. In this series, initial GH level was an

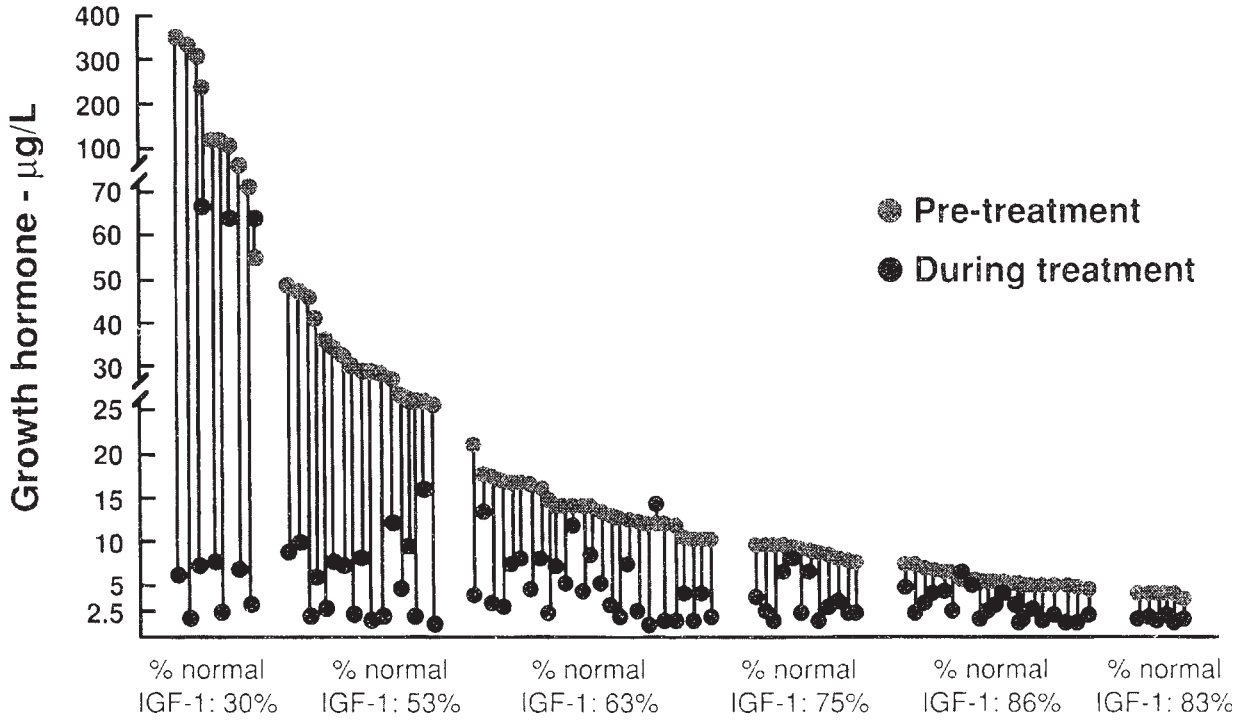

Fig. 3. IGF-1 improvement is related to pretreatment GH value.

important predictor of biochemical improvement with analog therapy. Mean GH (from 5-point GH profiles) improved to <2 µg/L in 100, 75, and 33% of patients, and IGF-1 normalized (to age- and gender-matched references) in 71, 60, and 0% of patients with entry GH of <25, 25–50, and >50 mU/L, respectively. In a larger study employing short-acting octreotide, there was also an inverse relationship between the initial serum GH and the response to therapy as judged by normalization of IGF-I concentrations (Fig. 3) *(25)*.

Where evaluated, no relationship was observed between pretreatment tumor volume and degree of tumor shrinkage *(37)*. Although the number of patients was small, only a weak correlation was seen between biochemical and radiologic responsiveness in the Bevan et al. *(39)* study, and no correlation was found between reduction in GH or IGF-1 and tumor regression in the series Newman et al. *(37)* or Colao et al. *(38)*. Thus, biochemical responsiveness does not at this point appear to be a surrogate for tumor regression.

What Is the Time Course of the Biochemical and Radiologic Responses? Are the Responses Sustained?

The biochemical response is rapid to short-acting octreotide but is delayed by ~14 d after the first dose of octreotide LAR. Most of the improvement in GH is achieved within 3 mo of initiating treatment, although a modest progressive decline is observed with continued therapy, and is sustained for as long as 48 wk *(38,39)*. Significant tumor regression has also occurred by 3 mo, and continued to decrease in size for up to 48 wk of therapy, although the rate of tumor shrinkage lagged behind biochemical improvement *(39)*. Imaging studies have not been performed earlier than 3 mo after initiation of therapy, so the role of somatostatin analog therapy for patients with tumor impinging on the optic chiasm awaits further investigation.

Do Side Effects Limit Somatostatin Analog Therapy?

Octreotide analog therapy is well tolerated by most patients. Side effects are similar among the available (long- and short-acting) somatostatin analogs and, in general, do not limit treatment. The most common side effects are gastrointestinal. Approximately half of patients experience diarrhea, nausea, or abdominal discomfort, which is transient in most patients. Approximately 30% of patients develop gallbladder sludge or microlithiasis, and about 15% of patients develop new gallstones, most of which remain asymptomatic. Other less frequent complications include abnormalities of glucose metabolism, injection site pain, transient hair loss, hypothyroidism, and sinus bradycardia *(24,33,37–39)*.

Can Recovery of Pituitary Function Accompany Primary Therapy with Somatostatin Analog Therapy?

Recovery of pituitary function may occur in as many as 30% of people having transsphenoidal surgery for macroadenomas *(72)*. Although recovery of pituitary function was not a primary end point of any of these studies, retrospective analysis of stored sera showed improvement in thyroid

and gonadal function in several patients, and absence of deteriorating pituitary function in others *(39)*.

Limitations of Primary Therapy with Somatostatin Analogs

Primary medical therapy with somatostatin analogs offers the prospect of clinical and biochemical improvement and substantial tumor shrinkage in a significant subset of patients with previously untreated acromegaly. Unfortunately, only 29% of patients achieved three end points of a GH <5 mU/L accompanied by IGF-1 normalization and >30% tumor shrinkage concurrently *(39)*. A significant minority of patients (range: 32–47%) do not normalize their IGF-1 levels and are therefore at risk for the morbidity associated with IGF-1 elevation. A more rapid and more robust reduction in tumor volume (as seen in the majority of patients with macroprolactinomas) would also be more desirable, in particular in individuals in whom there is threat to the optic chiasm. The relative costs of primary medical therapy compared to other treatment modalities is, of course, also a consideration but is beyond the scope of this review.

Current Recommendations for Use of Somatostatin Analogs as Primary Therapy

Surgery remains the therapeutic modality of choice for the relatively small subset of patients with microadenomas (~80% cure rate) and for those with well-circumscribed noninvasive macroadenomas. Of course, this recommendation must be individualized and take into account surgical risk, expertise, and patient preference. The strategy for patients with invasive macroadenomas is more problematic. Because ~40% of these patients will require medical therapy postoperatively, and because somatostatin analog treatment is equally effective in operated and nonoperated patients, a convincing argument can be made to defer surgery, and proceed directly to medical therapy. If biochemical cure is achieved, side effects are acceptable, and tumor volume is reduced (or at least not increasing), long-term medical therapy would be quite reasonable. If IGF-1 levels remain elevated, additional pharmacologic agents could be added to the regimen and their efficacy assessed. Surgery and/or radiotherapy would be logical interventions if side effects from medication are poorly tolerated, or if biochemical cure is not achieved or the tumor continues to enlarge while on maximal medical therapy.

Several special situations should also be considered. Primary medical therapy for people with visual compromise or tumor impinging on the optic chiasm should only be undertaken with extreme caution, until data become available regarding the rate at which tumor regression occurs, or agents that rapidly reduce tumor volume (analogous to efficacy of dopaminergic agents for prolactinomas) become available. An argument could also be made in favor of early surgical intervention in the case of a woman with a macroadenoma wishing to become pregnant, because data regarding the effect of somatostatin on a fetus are limited *(73,74)*. By contrast, the ~30% of individuals who cosecrete prolactin would be particularly amenable to a trial of medical management that includes a dopaminergic agonist as part of the regimen.

Future Directions

Further understanding of the molecular mechanisms responsible for the neoplastic transformation resulting in acromegaly will undoubtedly lead to the development of therapeutic agents that will enhance our ability to achieve predictable dramatic tumor regression in addition to biochemical cure. Further investigation is also needed to clarify the optimal use of currently available agents. This should include further assessment of the effect of somatostatin analogs used prior to surgery or in combination with radiotherapy *(75)*, the impact of surgical debulking on long-term somatostatin responsiveness, and evaluation of whether biochemical and radiologic improvements can be sustained if doses are reduced during long-term treatment. A role for the new SSTR-specific agents and investigation of optimal use of combination medical therapy with currently available agents (somatostatin analogs and GH-receptor blockers) *(76)* are also fertile ground offering the potential of improving the care of people with acromegaly.

Conclusion

The introduction of somatostatin analogs has had a major impact on the management of patients with acromegaly, resulting in improvement in clinical symptoms, biochemical parameters, and tumor regression in the majority of patients with micro- or macroadenomas. In addition to the use of somatostatin analogs as adjunctive therapy for people who have not been cured with surgery and/or radiotherapy, a role for the use of somatostatin analogs in previously untreated patients has emerged, providing a successful nonsurgical approach for a significant number of patients with acromegaly.

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