AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY DISEASE STATE CLINICAL REVIEW: MANAGEMENT OF ACROMEGALY PATIENTS: WHAT IS THE ROLE OF PRE-OPERATIVE MEDICAL THERAPY?

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ABSTRACT

Objective: Acromegaly is a complex disease characterized by growth hormone (GH) excess originating in most cases from a pituitary tumor. The goals of treatment include removing the tumor or reducing tumor burden, normalizing GH secretion and insulin-like growth factor 1 levels, and preserving normal pituitary function if possible. Surgery by an experienced neurosurgeon is still considered first-line therapy, especially in cases with small tumors. In the last few decades, significant progress in the development of selective pharmacologic agents has greatly facilitated the management of active acromegaly, with agents such as somatostatin-receptor ligands (SRLs), GH-receptor antagonists, and dopamine agonists. In addition to adjuvant treatment, pre-operative medical therapy and primary therapy in de novo patients are increasingly employed.

Methods: A United States National Library of Medicine PubMed search (through July 2014) was conducted for the following terms: acromegaly, pre-operative medical therapy, somatostatin-receptor ligands, and somatostatin analogs. Articles not in English and those not in peer-reviewed journals were excluded. In reviewing pertinent articles, focus was placed on biochemical and other postoperative outcomes of medical therapy.

Results: An analysis of the full effect of pre-operative use of SRLs on surgical outcomes (remission rates and peri-operative complications) is limited by heterogeneity of methodology, low overall surgical cure rates, and different study designs. The assumption that SRL use prior to surgery reduces peri-operative surgical risk has yet to be proven. A variable degree of tumor shrinkage with pre-operative SRLs is observed. Likewise, SRL treatment 3 months before surgery may improve surgical remission rates in the short term; however, positive results do not persist in the long term.

Conclusion: We consider that medical therapy before surgery could play a role in carefully selected patients, but treatment should be individualized. Primary medical therapy with a SRL may be considered in patients with macroadenomas without local mass effects on the optic chiasm, as SRLs have been shown to reduce tumor size and control GH hypersecretion. However, the data are insufficient to support general use of a SRL prior to surgery in order to improve post-surgery biochemical outcomes. Theoretically, patients with severe cardiac and respiratory complications due to acromegaly could potentially benefit from pre-operative SRLs in order to reduce peri-operative morbidity. Further investigation and investment in large randomized long-term clinical trials are needed to define the precise role and duration of pre-surgical medical treatment in acromegaly patients. **(Endocr Pract. 2015;21:668-673)**

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*The opinions represented in the **AACE/ACE Disease State Clinical Review: Management of Acromegaly Patients: What is the Role of Pre-operative Medical Therapy?** are the expressed opinions of the Neuroendocrine and Pituitary Scientific Committee of the American Association of Clinical Endocrinologists. AACE/ACE Disease State Clinical Reviews are systematically developed documents written to assist health care professionals in medical decision making for specific clinical conditions, but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment of the authors was applied.*

This review article is a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with, and not a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

Abbreviations:
GH = growth hormone; **IGF-1** = insulin-like growth factor 1; **MRI** = magnetic resonance imaging; **SRL** = somatostatin-receptor ligand

INTRODUCTION

Acromegaly is characterized by growth hormone (GH) hypersecretion caused in more than 95% of cases by a pituitary somatotroph adenoma (1-8). Morbidity and mortality associated with acromegaly are due to metabolic consequences of GH and insulin-like growth factor 1 (IGF-1) hypersecretion and direct mass effects from the somatotroph adenoma (6). Goals of treatment include removing the tumor or reducing tumor burden, normalizing GH secretion, and preserving normal pituitary function, if possible (2,7,9).

Complications linked to acromegaly are principally premature atherosclerosis, hypertrophic cardiomyopathy, diabetes mellitus, arthritis, sleep apnea syndrome, and polyps of the colon (6-8). Recent studies have shown that many of these complications (though not all) can be improved, at least in part, with appropriate therapy. In addition, biochemical remission after treatment may also reverse the apparent increased risk of mortality in patients with acromegaly (10,11).

Transsphenoidal surgery to remove the GH-secreting pituitary adenoma is usually first-line therapy (2,3,6,9,12). However, even with an experienced neurosurgeon, not all patients achieve a surgical remission (7). Over the last decade, there have been important advances in medical therapy to treat acromegaly (7,12). Three classes of pharmacologic agents are routinely used to control the disease: somatostatin-receptor ligands (SRLs) and dopamine agonists (e.g., cabergoline) that suppress the secretion of GH from the pituitary tumor, and a GH-receptor antagonist (2,3,6,12). SRLs are considered the mainstay of medical therapy (1-6) when used either as adjuvant or primary medical therapy.

In this review, we will address the potential benefit of use of pre-operative medical therapy to improve surgical endpoints. As the large majority of studies regarding pre-operative therapy for acromegaly involve the use of SRLs and not of a dopamine agonist or GH-receptor antagonist, the focus of this review will be on patients with acromegaly who received pre-operative therapy with SRLs.

METHODS

A United States National Library of Medicine PubMed search (through July 2014) was conducted for the following terms: acromegaly, pre-operative medical therapy, somatostatin-receptor ligands, and somatostatin analogs. Articles not in English and those not in peer-reviewed journals were excluded. In reviewing pertinent articles, focus was placed on biochemical and other postoperative outcomes of medical therapy.

RESULTS

Pre-operative Use of SRLs and Improvement in Biochemical Control (GH and/or IGF-1) after Surgery

In the late 1980s, the observation that SRL treatment was associated with improvement in both hormonal secretion and signs and symptoms of the disease, coupled with possible tumor shrinkage, led to several pre-operative trials, with attempts to influence surgical outcomes (13,14). In a large series, Stevenaert and Beckers (14) compared 48 patients treated with subcutaneous octreotide with 104 patients who were not pretreated and found that disease control was significantly improved post-operatively for patients with both microadenomas and enclosed macroadenomas. The authors also noted that tumors were soft after medical treatment and therefore easier to resect. Nonetheless, subsequent studies reported conflicting results regarding improvement in biochemical control (15-17). Interestingly, in nearly all studies, symptomatic improvement, variable tumor shrinkage, and morphologic changes at the tumor level were reported in patients who were pretreated with a SRL (15-17).

The majority of these studies included patients treated with a short course of rapid-acting SRLs pre-operatively; very few were prospective and none were randomized or controlled. Variations in the GH and IGF-1 assays and definitions of normal changed over time, thus complicating one's ability to assess study efficacy (18,19).

To date, 6 prospective studies have been published, 4 randomized (with at least 3 months of SRL pre-operative treatment) and 2 non-randomized (see Table 1). In the study by Carlsen et al (20), 62 subjects were randomized to surgery or to pretreatment with the long-acting SRL, octreotide LAR, 20-mg monthly for 6 months prior to surgery. Biochemical control was defined by normalization of serum IGF-1 at 3 months following surgery. The surgical remission rate in pretreated patients with macroadenomas (50%) was significantly higher than in the untreated group (16%), but the statistical significance vanished if remission criteria included both IGF-1 and GH normalization (defined as GH nadir less than 1 ng/mL). The absence of any effect of octreotide pretreatment in patients with microadenomas may be explained by the low number of microadenomas in the study but could also be due to the relatively low cure rate in this multicenter study. Based on previous dose-optimization reports (2,21,22), it is possible that a higher dose of octreotide LAR or a longer duration of treatment might have achieved improved biochemical control overall. In contrast to studies that reported that

the tumors were softer and easier to resect after medical treatment, the surgeons in the study by Carlsen et al (20) reported that the tumors in the pretreated group were firmer. Firmness of the tumor did not correlate with biochemical outcomes 3 months after surgery. Long-term follow-up data have been published on these subjects (23). When the authors used a combined IGF-1 and GH criterion for cure, there was no statistical difference in biochemical control between the pretreated and non-pretreated groups: 10 of 26 (38%) macroadenomas were cured in the pretreatment group compared with 6 of 25 (24%) in the direct surgery group at 1 year postoperatively and 9 of 22 (41%) versus 6 of 22 (27%) macroadenomas 5-years postoperatively (23).

Other randomized studies have analyzed the effects of pre-operative treatment solely in patients with macroadenomas (24,25), using lanreotide SR for 3 to 4 months (24,25) or octreotide LAR for 3 months (24). In the study by Mao et al (26), 24 of 49 (49 %) pretreated patients achieved remission at 4 months postoperatively versus 9 of 49 (18.4%) patients who underwent surgery without SRL pretreatment. Similar results were observed by Li et al (25) in patients harboring invasive pituitary adenomas; patients in the pretreated group had a significantly higher remission rate: 45.8% versus 20% ($P<.05$) as determined by a combination of normalized IGF-1 and a GH nadir less than 1.0 μg/L after oral glucose tolerance testing. The "firmness" of the tumor during surgery was again noted as increased (24). However, further large prospective studies are needed to determine the tumor consistency after medical treatment. Mean tumor shrinkage rate in the study by Shen et al (24) was almost 40% in the pretreated group (albeit with a large standard deviation), and GH and IGF-1 levels were lower at both 3 months and 6 months after surgery (24). Interestingly, in the patients treated with octreotide LAR before surgery, the total resection rate was higher in patients whose Hardy-Knosp grading decreased to ≤2 (tumor extends beyond the median line of the cavernous sinus, but does not extend beyond to its lateral line) compared with those whose Hardy-Knosp grading was still ≥3 (extension beyond lateral line or totally wrapped around the intracavernous carotid artery) after drug pretreatment.

In a meta-analysis, Pita-Gutierrez et al (27) analyzed 10 studies (5 retrospective studies with a control group, 2 prospective nonrandomized trials, and 3 prospective controlled trials) and examined the biochemical postoperative cure rate in pretreated patients. A borderline effect was detected in the analysis of all trials with control groups, with a pooled odds ratio (OR) for biochemical cure with SRL treatment of 1.62 (95% confidence interval [CI], 0.93 to 2.82). However, analysis of the 3 prospective randomized trials demonstrated a clear significant improvement (albeit at short-term follow-up) in the pretreated groups: OR, 3.62 (95% CI, 1.88 to 6.96). Of note, several of the randomized studies have reported unusually low remission rates in their surgical control groups, raising doubt about the generalizability of study findings. The loss of statistical significance when both randomized and nonrandomized trials have been included could be also due to different inclusion criteria in the nonrandomized trials; thus, patients with higher GH/IGF-1 values and larger tumors being preferably pretreated.

Predictive factors for response to pre-operative SRL treatment are lacking. Puig-Domingo et al (28) showed initially that a hypo-intense T2-weighted magnetic resonance imaging (MRI) signal is associated with a better response to adjuvant SRLs at 6 and 12 months in patients after surgery. Furthermore, recent studies showed that T2 signal intensity on MRI at diagnosis correlates with histologic features and predicts biochemical outcome of first-line SRL treatment (29). Further studies are needed to determine the role of MRI in the treatment decision algorithm for pre-operative medical therapy.

Longer-term data (≥12 months) on patients treated pre-operatively with SRLs were not available until recently (23,24). In the study of Fougner et al (23), no long-term improvement in cure rate by pretreatment at either 1 year or 5 years was found. However, when data were combined with biochemical values at last follow-up for patients with invasive adenomas (24), there was a nonsignificant trend toward improved surgical control (23). Notably, the total number of pretreated patients with available long-term data was <100. These results were replicated in a different meta-analysis (30), which showed a short-term improvement in the pretreated group but no significant difference over the long term. A possible explanation could be carryover effects of the SRLs (18,31-34), which persist for a few months postoperatively, hence potentially leading to falsely higher short-term rates of remission in pretreated patients (18,19).

Immediate Postoperative Outcomes: Rates of Postsurgical Complications, Duration of Hospital Stay

Patients with acromegaly are thought to have higher risk of anesthesia morbidity compared to patients with other types of pituitary adenomas, mainly related to hemodynamic changes and an increased incidence of difficult intubation (35-38). However, Seidman et al (39) evaluated 29 acromegaly patients who underwent general anesthesia compared to age-matched controls and found no difference in the amount of vasoactive drugs required or in arterial oxygen or carbon dioxide tension. Although acromegaly patients had altered intra-operative parameters compared to controls, there was no increased cardiovascular or pulmonary morbidity in this study. In a single-center study, Friedel et al (35) focused on airway management and noted that videoscopic direct laryngoscopy intubation was required in 7 of 32 patients and fiberoptic intubation in 4 of 32 patients with acromegaly. These data are similar to that of the study by Schmitt et al (38), in which 26% of patients

Table 1
Summary of Remission Rates in Acromegaly Patients with Macroadenomas Pretreated with Somatostatin-Receptor Ligands (SRLs) before Surgery in Published Prospective Randomized Clinical Trials[a]

Reference	Number of patients: macroadenomas	Duration of pre-operative SRL treatment (weeks)	Postoperative assessment (months)	Short-term remission (3-4 months after surgery)		*P* value	Long-term remission (6-60 months after surgery)		*P* value
				SRL-treated group	Nontreated group		SRL-treated group	Nontreated group	
Carlsen (20)	51	24	3	50%	16%	.01	-	-	-
Carlsen (20)	10 invasive	24	3	25%	0%	NS	-	-	-
Shen (24)	39	24	6	-	-	-	47.4%	20%	.03
Mao (26)	78	12	4	50%	21%	.00	-	-	-
Mao (26)	20 invasive	12	4	55.5%	9%	.00	-	-	-
Li (25)	49	12	3	54.2%	24%	.02	-	-	-
Fougner (23)	61 (17 had postoperative adjuvant medical therapy before 1 year)	12	12	-	-	NA	46%	32%	NS
Fougner (23)	28	12	60	-	-	-	43%	35%	NS

Abbreviations: NA = not applicable; NS = not significant
[a] Fougner et al (23) study displays long-term results for the patients included originally in Carlsen (20). Data are shown in all studies for normalization of serum insulin-like growth factor 1 as the definition of remission. Tumors have been defined as invasive when cavernous sinus invasion was noted on magnetic resonance imaging.

with acromegaly were noted to have difficulty with laryngoscopy during planned surgical intervention.

Risk of cardiac complications in patients with acromegaly are well known, including, but not limited to, left ventricular hypertrophy, increased stroke volume and cardiac index, ventricular dysrhythmias, biventricular cardiomyopathy, and heart failure (6,7,12,40-42). Despite clear favorable effects of SRLs on cardiac function (41,42), the beneficial outcome on cardiac complications in patients treated pre-operatively has not been demonstrated.

DISCUSSION

An analysis of the full effect of pre-operative use of SRLs on surgical outcomes (remission rates and peri-operative complications) is limited by heterogeneity of methodology, low overall surgical cure rates, and different study designs. The assumption that SRL use prior to surgery reduces peri-operative surgical risk has yet to be proven. A variable degree of tumor shrinkage with pre-operative SRLs is observed. Likewise, SRL treatment 3 months before surgery may improve surgical remission rates in the short term; however, positive results do not persist in the long term. In summary, pre-operative medical treatment theoretically improves acromegaly symptoms, decreases arterial stiffness and improves endothelial function, reduces soft tissue swelling, particularly in upper airways, and induces better blood pressure control, thus potentially leading to decreased anesthesia complication rates and lower surgical risk (43,44). However, based on the limited data (16,24), SRLs have not been shown to improve anesthetic risks per se or decrease rates of surgical complications, panhypopituitarism, or hospital stay duration. The effects of SRLs on glucose metabolism are complex; SRLs increase insulin sensitivity but also decrease secretion of glucagon and insulin (1-6). The decreased rate of cerebrospinal fluid leaks in the pretreated patients in the study by Shen et al (24) is of interest but has not been replicated elsewhere.

If a decision is made to treat a patient before surgery with the goal to improve biochemical control after surgery, the optimal treatment duration is unknown, and practice varies between different Pituitary Centers. It has been shown that near maximum biochemical improvement and tumor shrinkage could be observed within 3 months, if the SRL dose is maximized at the time the study starts (19,43,45).

CONCLUSION

Based on available data, the advantage of a SRL to improve surgical outcomes or reduce peri-operative morbidity and mortality is unclear. Prospective studies have not demonstrated a definite benefit of SRLs on

surgical efficacy, especially in the setting of macroadenomas. Patients with severe cardiac and respiratory disease could also benefit from a short SRL course before surgery, but there have been no reported differences in surgical complication rates or hospital stays comparing pretreated and non-pretreated patients in published studies.

If determinants of individual tumor responsiveness could be identified in the future, clinicians will be able to tailor specific therapy to each patient to optimize both peri-operative and postoperative clinical outcomes. Cost-effective analyses would also generate information critical to decision making.

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