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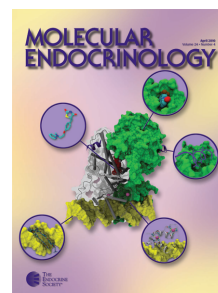
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Does Preoperative Somatostatin Analog Treatment Improve Surgical Cure Rates in Acromegaly? A New Look at an Old Question

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A cromegaly is caused in most cases by chronic GH hypersecretion from a pituitary adenoma. Typically, acromegaly has an insidious onset, with patients often suffering from unrecognized signs and symptoms for up to a decade before diagnosis (1). Apart from the characteristic physical changes to the face and extremities, patients with acromegaly are at increased risk for cardiac disease and colorectal cancer (2–4). Retrospective cohort studies show that chronic GH hypersecretion increases mortality, which can be returned to normal with effective control of GH and IGF-I (5, 6). Surgery, usually via the transsphenoidal route, is first-line therapy for acromegaly in suitable and willing patients. The surgical cure rate is 70–85% for noninvasive microadenomas and enclosed (noninvasive) macroadenomas, and for large macroadenomas and invasive tumors, the cure rate is lower (20–50%); the overall cure rate is in the region of 55–65% (7). The expertise of the surgeon is a crucial element in the outcome of acromegaly, with dedicated pituitary neurosurgeons having better results (8).

Somatostatin analogs (SSAs) are the main medical treatment for acromegaly, and some centers have more than 20-yr experience with these compounds. In general, SSAs are used as an adjuvant therapy in patients whose symptoms and hormone abnormalities are not completely controlled by surgery. Primary therapy with a SSA is increasing in popularity, particularly among elderly or infirm subjects, or among those unwilling to undergo surgery. Adjuvant SSA therapy normalizes GH and IGF-I in 49–56% and 48–66% of patients, respectively (9). Primary SSA treatment controls GH and IGF-I in approximately 50 and 60% of patients, respectively. SSAs are also associated with tumor shrinkage in acromegaly, with approximately 37% of patients showing some decrease in tumor size during primary medical therapy (10), and 21% of those receiving adjuvant SSA treatment (11). This tumor shrinkage does not appear to be due to tumoricidal or strong pro-apoptotic effects but, rather, to a

complex pattern of morphological alterations within the tumor that include decreases in secretory granule number and capacity and fibrosis (12, 13).

Apart from tumor size/invasiveness and surgical expertise, few other factors influence improved cure rates in acromegaly. One factor that has been studied repeatedly is the preoperative use of SSAs to try to improve the subsequent surgical cure rate. The combination of improved hormone secretion, decreased symptoms/signs, and tumor shrinkage led to the preoperative use of SSAs in some centers as early as the 1980s (14, 15). In a large series, we compared postoperative biochemical outcome in 48 patients who were pretreated with octreotide compared with 104 patients who did not receive SSAs (16). Tumor shrinkage occurred in 56.5% of pretreated patients with marked shrinkage (>25%) being seen with longer duration of SSA therapy. Disease control occurred at a significantly higher rate in pretreated patients with microadenomas or enclosed (noninvasive) macroadenomas as compared with nonpretreated patients. Overall, adenomatous tissue was soft and easy to remove among the pretreated group. Many other groups have examined the issue of pretreatment since these early studies. Whereas some large series support the value of treating with a SSA before surgery, other groups have demonstrated no clear value, although symptomatic improvement, tumor shrinkage, and morphological changes have been validated (17–19).

The discrepancies among the studies have led to uncertainty regarding whether pretreatment of surgical candidates leads to improved control of acromegaly. As such, none of the previously mentioned studies was ideally designed, nor does any provide definitive data. An ideal study should be a prospective randomized controlled trial that includes a large number and variety of patients with acromegaly in both treatment arms. In addition, patients should be evaluated preop-

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Abbreviation: SSA, Somatostatin analog.

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eratively by a single endocrinology-radiology team to ensure balance between the pretreated and nonpretreated groups before being operated upon by a single pituitary neurosurgeon. Finally, disease response should be evaluated not only 3 months after surgery/withdrawal of a SSA, but also 1 yr later to exclude any lingering effect of presurgical SSA treatment on the outcome.

Such a strict design has militated against a definitive work. Thankfully, however, in this issue of the *Journal*, Carlsen *et al.* (20) deal substantively with this difficult topic. The authors performed a multicenter study in Norway investigating whether 6 month preoperative octreotide treatment improved the surgical outcome in newly diagnosed acromegalic patients. They assembled a sizeable cohort ($n = 62$) that was randomized to either directly undergo transsphenoidal surgery ($n = 30$) or receive im octreotide LAR 20 mg every 28 d for 6 months ($n = 32$). They showed that a higher proportion of pretreated subjects (45%) were cured by surgery (as defined by IGF-I normalization) as compared with those that did not receive octreotide (23%). Furthermore, the surgical cure rate was significantly higher after pretreatment among subjects with macroadenomas (50%) *vs.* the nonpretreated group (16%). To that extent, this new prospective study provides strong support for pretreating patients with acromegaly with a SSA for 6 months.

However, on closer inspection some issues remain. When the authors defined a cure using both GH and IGF-I, the statistical significance favoring pretreatment with octreotide disappeared, although the results remained numerically in favor of the pretreatment group. In patients with microadenomas, pretreatment had no appreciable effect, although these conclusions are limited by the very small number of patients with microadenomas. At variance with much of the published literature, Carlsen *et al.* (20) noted that firmness of tumors was common among the pretreated group. In addition, the authors did not address whether octreotide pretreatment facilitated subsequent tumor removal. Previous studies have noted that SSA pretreatment was associated with a softening of the tumor and easier removal due to clear differences in consistency as compared with the adjoining normal pituitary tissue. Whatever the effect of SSA on tumor consistency (a subjective evaluation by the neurosurgeon), there is general agreement that tumor shrinkage in large tumors can bring portions of the tumor into the operative field that would otherwise have remained hidden or inaccessible.

Despite expected symptomatic improvement and reduction in soft tissue swelling, SSA pretreatment altered neither the overall surgical complication rate nor the duration of hospital stay. It would have been very useful to assess anesthetic risk grades and cardiovascular status in the SSA pretreated and surgery only subgroups to determine whether SSAs had a clinically relevant effect on overall preoperative health status, as has long been suspected. The surgical cure rate in this study was rather low in comparison with the rates reported widely in the literature. This may have been an effect of the relatively low number of microadenomas included. However, the multicenter nature of the study may have led to some variations in

surgical practice across the centers. Although a single center study would have been ideal, only a handful of the largest pituitary treatment centers worldwide could possibly recruit a similar patient population in a timely manner. Finally, the evaluation for hormonal control was performed 3 months postoperatively. Although this is the minimum accepted “safe” period to allow for washout of SSA effects, it would have been more clinically meaningful to report cure and control rates over the long term. One year postoperative data would definitively exclude any persistent effect of SSAs in the pretreated group. Indeed, a follow-up study of this cohort at 1 yr and beyond would help determine whether the beneficial effect of preoperative SSAs on surgical outcomes endures for the longer term.

Despite these caveats, the findings reported by Carlsen *et al.* (20) support the view that SSA pretreatment may allow for greater long-term cure rates in subjects with acromegaly. Such an effect would have clear benefits not only for the patient but also in terms of optimizing health care resource utilization.

Acknowledgments

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