Treatment Options for Acromegaly

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Treatment options for acromegaly include surgical removal of the adenoma, radiotherapy, or pharmacological reduction of growth hormone (GH) levels by dopamine agonists or somatostatin analogs. Whether such treatment can truly cure acromegaly is debatable. A problem with evaluating efficacy of treatment is the lack of consensus of what constitutes a cure. Despite modern neurosurgical techniques for resecting GH-secreting pituitary adenomas, more than 50% of patients may have persistent GH hypersecretion; radiotherapy may take years to produce an effect. There is thus interest in pharmacological relief of symptoms and reduction in GH secretion. We report on eight patients with a biochemical diagnosis of acromegaly (failure of suppression of GH levels to < 2.5 μg/L following a glucose tolerance test [GTT]). The use of Sandostatin-LAR® (Sandoz Pharma Ltd, Basel, Switzerland) in doses of 20 to 30 mg intramuscularly at 4 week intervals produced consistent and therapeutic serum octreotide concentrations, suppressed GH secretion to 5 μg/L in all eight subjects, lowered insulin-like growth factor-1 (IGF-1) levels in all and normalized values in seven of eight, improved or led to disappearance of symptoms and signs, and was not associated with an increase in adverse events as compared with subcutaneous treatment.

ACROMEGALY is an uncommon condition (prevalence, 40 to 60 per million) resulting almost invariably from a growth hormone (GH)-secreting pituitary adenoma. The condition is symptomatically disabling and is associated with an increased mortality rate due to excess deaths from cardiac, respiratory, and malignant diseases.[1] The primary aims of treatment are clear: remove symptoms, reduce tumor bulk, and prevent regrowth of tumor. In view of recent evidence that reduction of GH levels may be associated with reduced mortality,[2,3] additional benefit may be achieved by restoring GH dynamics to normal.

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One of the problems with evaluating efficacy of treatment is the definition of what constitutes a cure, and there is no real consensus about this definition. However, what most clinicians would accept would be the following: (1) mean serum GH level less than 2.5 μg/L (random values or single-day measurements); (2) glucose tolerance test (GTT) suppression to a GH level less than 1 μg/L; and (3) normal insulin-like growth factor-1 (IGF-1) levels. However, despite this, it is clear that treated acromegalic patients whose GH dynamics have been normalized according to these criteria have been shown to secrete abnormally frequent pulses of GH.[4]

It is important to know how well we do in achieving these targets. Our own retrospective analysis of 89 acromegalic patients (68 macroadenomas) treated between 1985 and 1994 indicated that only 53 of 89 patients (60%) had a most recent random GH level less than 5 μg/L and only 35 of 89 (39%) had a value less than 2.5 μg/L.

Despite this relatively poor success rate, the frequency of hypopituitarism was high (78%) and there was no association between the development of hypopituitarism and achieving a GH level less than 2.5 μg/L or less than 5 μg/L. These observations are particularly relevant in view of data demonstrating increased mortality in hypopituitary patients, particularly due to cardiovascular disease.[5]

Thus, despite modern neurosurgical techniques for resecting GH-secreting pituitary adenomas, more than 50% of patients may have persistent GH hypersecretion[6]; in addition, radiotherapy may take several years to produce an effect. There is, understandably, considerable interest in the pharmacological control of GH, with the objectives of relieving symptoms and reducing GH secretion. Somatostatin is an endogenous hypothalamic peptide that inhibits GH release from the anterior pituitary, but which has a very short half-life of 1 to 3 minutes. Octreotide (Sandostatin®; Sandoz Pharma Ltd, Basel, Switzerland) is a long-acting synthetic somatostatin analog (half-life, 80 to 100 minutes) that was first used to treat acromegaly in the mid 1980s.[7] Subsequent studies indicate that the drug is effective, with GH levels decreasing in 94% of patients treated (to <5 μg/L in 45% of cases).[8,9] IGF-1 levels decreased in 92% of patients treated and were normalized in about 50% of cases. Of interest was that tumor size was shown to be decreased by more than 20% in 15 of 34 patients studied prospectively (44%).

A review of the published data suggests that the administration of subcutaneous Sandostatin® results in an improvement in clinical symptoms in approximately 80% of subjects, a decrease in GH in approximately 80%, and GH values less than 5 μg/L in 40% to 50%. Currently, octreotide is given subcutaneously three times daily, although evidence is accumulating that for a given dose of the drug, continuous infusions are more effective than subcutaneous regimens. This observation, along with the inconvenience of three-times-daily administration, has led to the development of depot preparations. The data presented here relate to the development of one of these—Sandostatin-LAR®.

The objectives of developing such a preparation were to achieve a once-a-month injection, stable serum octreotide concentrations, good clinical control of symptoms and signs, sustained GH and IGF-1 suppression, and good acceptability and compliance. Sandostatin-LAR® is a formu-

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lation that has incorporated octreotide in microspheres of the biodegradable polymer poly (DL-lactide-co-glycolide). A similar preparation of bromocriptine (Parlodel-LAR®; Sandoz Pharma) has been used to treat patients with prolactinomas and acromegaly. Preliminary data have shown that Sandostatin-LAR® produces sustained elevated levels of octreotide in contrast to the peaks and troughs seen with the subcutaneous regimen. The aim of this study was to evaluate the efficacy, tolerability, and pharmacokinetics of Sandostatin-LAR® in the treatment of acromegaly.

Data reported here are on eight patients. All patients had presented with symptoms and signs of acromegaly and a biochemical diagnosis had been made by failure of suppression of GH levels to less than 2.5 μg/L following a GTT. No patient had received radiotherapy in the previous 12 months. Four patients had macroadenomas and two had not been treated with either surgery or radiotherapy. The study had full approval from the local ethical committee and all patients gave written informed consent. Initially, all patients were treated with Sandostatin® three times a day subcutaneously for a minimum of 4 weeks, and all showed a decrease in mean GH levels by 50%. After a 14-day washout period, Sandostatin-LAR® was administered as a single depot intramuscular injection.

The study protocols were complex, but allowed for evaluation of the patients over an extended period when they all received 12 injections. Data from mean 12-hour profiles over 60 days following the first injection showed low levels of serum octreotide up until day 7, which then increased to high levels by day 14, remaining elevated for the subsequent 3 weeks. GH levels decreased after day 7, remaining significantly suppressed until day 21 to 28. By day 60, GH was increasing in six of eight patients. On the basis of data from the first two injections, the following revisions were made. No patient was to receive the 10-mg dose. An interval of 60 days was considered to be too long, particularly when taking into account the 7-day lag period after injection. Thus, four patients received either 20 or 30 mg every 42 days, and four patients 30 mg every 28 days.

Data from the following 12 injections showed that GH was significantly lowered in the group as a whole after the third injection and suppression was maintained until the end of the study. GH was suppressed to less than 5 μg/L in every patient and to less than 2.5 μg/L in five of eight patients. The mean nadir value was 2.6 μg/L.

Serum IGF-1 values decreased in the group as a whole from 927 ng/mL at baseline to 472 ng/L by the end of the sixth injection. IGF-1 was normalized (500 ng/mL) in seven of eight patients. As a group, serum octreotide levels increased from 630 and 765 pg/mL at the end of injections 1 and 2, to 1,311, 1,331, and 1,455 pg/mL at the end of injections 4, 5, and 6, respectively. These compare with values of 2,040 pg/mL after 4 weeks of subcutaneous Sandostatin®; thus, with patients taking 20 to 30 mg every 28 to 42 days, no evidence of octreotide accumulation was seen.

The administration of Sandostatin-LAR® resulted in a significant improvement in headache, sweating, and arthralgia. Three patients complained of parasthesiae in both hands at baseline and this disappeared with treatment. Fatigue improved, although this did not achieve statistical significance. Moderate discomfort at the injection site lasting for less than 24 hours was seen in 7% of all 96 injections administered, with mild discomfort in 23%. No problems of flare or swelling at the injection site were observed. Gastrointestinal side effects were transient and mild. Four of eight patients experienced mild abdominal cramps after injections 1 to 3. Ultrasounds of the gallbladder were performed before and during treatment and, although asymptomatic gallstones have previously been reported in 25% to 50% of patients receiving subcutaneous octreotide,[10] no gallstones have occurred to date in this study in eight patients after 12 injections of Sandostatin-LAR®. One patient had a gallbladder polyp at diagnosis, which did not change in size. One patient developed the ultrasonographic appearance of "sludge" after six injections.

CONCLUSIONS

Sandostatin-LAR® is therefore an effective and well-tolerated treatment for acromegaly. The main indication still remains the patient who is not cured following pituitary surgery and/or radiotherapy. Ultimately, the cost-effective analysis and clinical outcome of long-term Sandostatin-LAR® versus pituitary surgery will have to be made, but further studies should address whether this drug has a role to play as first-line therapy for some acromegalics, such as those in which the disorder is due to a pituitary microadenoma.

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