The Role of Somatostatin Agonistic Analogs in the Treatment of Acromegaly

George Tolis

Acromegaly mainly associated with the presence of a growth hormone (GH)-secreting pituitary tumor causes considerable morbidity and carries a risk of premature mortality. Treatment includes surgery, radiotherapy, and the use of dopaminomimetic drugs and somatostatin agonist analogs (octreotide and lanreotide). The use of long-acting somatostatin analogs is limited to adjuvant therapy following failure of surgery and/or radiotherapy and/or bromocriptine. But it may be considered the drug of choice for childhood acromegaly and for syndromes of plurihormonal pituitary overproduction in association with excess GH-releasing hormone (GHRH) and a McCune/Albright-like syndrome. Octreotide has been administered de novo as primary and/or presurgical preparatory therapy. Octreotide doses of 100 to 1500 μg were used in two large series in Europe and the United States, which mainly included acromegalics in whom all other modalities had failed (>65%). Clinical improvement, which was sustained for over 6 months of follow-up evaluation, was reported for more than 50% to 70% of patients. In evaluable patients with visual-field defects, there was a definite amelioration, even if the tumor mass was not reduced, and there was no worsening during therapy; the same is true for the adenoma mass, which showed a variable reduction (median, 15 to 22%). A reduction of serum GH and insulin-like growth factor-1 (IGF-1) levels was found in more than 90% of patients, with GH serum values <5 ng/mL and IGF-1 serum values <2 U/mL recorded in 46% and 49%, respectively. Relapse occurred when treatment stopped. Future developments are expected to improve the clinical usefulness of somatostatin analogs.

ACROMEGALY mainly associated with the presence of a growth hormone (GH)-secreting pituitary tumor should be treated as soon as possible, because it causes considerable morbidity and carries a risk of premature mortality. Headache, hypertension, musculoskeletal disorders (such as osteoarthritis, carpal tunnel syndrome, and muscular weakness), metabolic derangements (eg, diabetes mellitus and dyslipidemia), and CNS dysfunctions expressed as somnolence and depressive reaction, can make life miserable, whereas premature death occurs due to an increased prevalence of cerebro/cardiovascular, respiratory, and malignant diseases.

Therapy aims to control symptomatology, normalize hormone hypersecretion (while preserving the rest of the pituitary function), minimize the inadvert sequelae leading to increased morbidity, reduce or dissolve tumor mass, and prevent its regrowth. Treatment modalities include surgery and radiotherapy, and the use of pharmaceutical biological response modifiers such as dopaminomimetic drugs and somatostatin agonist analogs (octreotide and lanreotide).

Surgical removal of a pituitary microadenoma (total selective) is the ideal mode of therapy, but is not always feasible due either to limited expertise and/or to the tumor being large and extending to parapituitary and suprapituitary areas.

Radiotherapy has been tried both as a primary therapy, when microneurosurgery was not that advanced, or as the adjuvant after surgery has failed to extirpate the disease; yet its overall success has not been impressive and it is associated with nonnegligible morbidity and mortality. Even recent advances with stereotactic approaches and other high-tech equipment (the availability of which is limited) has not been convincing in its efficacy.

Thanks to the advances of neuropharmacology and peptide chemistry, bromocriptine—as a typical dopaminomimetic—and somatostatin were shown to be capable of decreasing excess GH secretion. Long-term studies show that the former, although reported to exert an improvement in the symptoms/signs of acromegaly, was associated with considerable side effects (when administered in the required large doses), but also did not result in normalization of GH and insulin-like growth factor-1 (IGF-1) in as many as 90% of patients. However, the synthesis of octreotide by Sandoz researchers, and later of lanreotide, by the collaboration of investigators at Tulane University and Ipsen Laboratories, opened new vistas in the treatment of acromegaly; more importantly, these drugs have been made available worldwide. Our group and numerous others began clinical trials as early as 1982, which led to an explosion of information, distributed and printed initially with the support of Sandoz and the European Neuroendocrine Association and in subsequent publications,[1-16] which reflected the experience of many in Europe and the United States, respectively. Currently as far as acromegaly is concerned, the use of long-acting somatostatin analogs is limited to adjuvant therapy following failure of surgery and/or radiotherapy and/or bromocriptine, and has been proven to be most effective. In addition, it seems to be the drug of choice for childhood acromegaly (where, for reasons not fully understood, surgery is rarely successful), as well as for syndromes of plurihormonal pituitary overproduction in association with excess GH-releasing hormone (GHRH) and a McCune/Albright-like syndrome.

Octreotide has been administered de novo as a primary and/or presurgical preparatory therapy, as well as in cases of surgical and/or radiotherapy failure. Octreotide doses of 100 to 1500 μg were used in two large series in Europe and the United States, which mainly included acromegalics in whom all other modalities had failed (>65%). Clinical improvement, which was sustained for over 6 months of close follow-up evaluation, was reported for greater than 50% to 70% in relation to specific symptoms/signs. In evaluable patients with visual-field defects, there was a

From the University of Athens, Athens, Greece.

Address reprint requests to Professor George Tolis, MD, Director of the Division of Endocrinology, Hippokrateion Hospital, 114 Vas Sophias Ave, Athens 11527, Greece.

0026-0495/96/4508-1014$03.00/0

definite amelioration, even if the tumor mass was not reduced, and there was no worsening of the tumor mass during therapy; the same is true for the adenoma mass, which showed a variable reduction, with a median of 15% to 22%, but never grew during treatment with octreotide. The improvement of clinical symptoms and signs, ie, acral growth, ring size reduction, and hypertension, was also evident in GH and IGF-1 levels. A reduction of serum GH and IGF-1 levels was found in more than 90% of patients, while GH serum values less than 5 ng/mL and IGF-1 serum values less than 2 U/mL were recorded in 46% and 49% of the patient population, respectively. Unfortunately, discontinuation of therapy resulted in reappearance of the clinical picture of acromegaly, along with an increase in serum GH and IGF-1 levels. In a few instances, despite continued therapy, there was a slow but steady increase in serum GH and IGF-1 levels. In all patients, there were some transient and some more sustained side effects.

Therefore, could and should one use the analogs as primary therapy, and what may one expect in the future? The available data support the hypothesis that somatostatin analogs do have a role as primary therapy, but such a use is limited by a few considerations. The first consideration is the cost and the need for life-long administration. Second, there are side effects arising via a spill-over effect on receptors of the diffuse neuro-gut axis; selective agonists will hopefully be developed following the identification of specific receptor subtypes. Indeed, our screening of two such compounds indicated that one seemed to be inhibitory mainly for GH release, having a negligible effect on insulin secretion (in contrast to octreotide). Third, the unavailability, as yet, of approved analogs with a prolonged duration of effect, like the GnRH analogs with a 3 months' duration of effect, must be taken into account. Such future developments are expected, especially if at a low cost, not only to enhance the patient's and physician's harmonic relationship, but also to provide acceptable safety profiles. Finally, radiolabeling of specific receptor subtype agonistic analogs may further enhance diagnostic accuracy and provide specific bullets for the control of remote lesions.

REFERENCES

1. Growth Hormone, Growth Factors and Acromegaly, in Lüdecke D, Tolis G (eds): Progress in Endocrine Research and Therapy, vol 3. New York, NY, Raven, 1987
2. Acromegaly: A century of scientific and clinical progress, in Robbins RJ, Melmed S (eds): Proceedings of the Acromegaly Centennial Symposium, Serono. New York, NY, Plenum, 1987
3. Cushing H: Partial hypophysectomy for acromegaly: With remarks on the function of the hypophysis. Ann Surg 50:1002-1017, 1909
4. Tolis G, Yotis A, Del Pozo E, et al: Therapeutic efficacy of a somatostatin analogue (SMS 201-995) in active acromegaly. J Neurosurg 65:37-40, 1986
5. Nabarro JDN: Acromegaly. Clin Endocrinol (Oxf) 26:481-512, 1987
6. Tolis G: Long term management of acromegaly with sandostatin. Horm Res 29:112-114, 1988
7. Barkan AL, Lloyd RV, Chandler WF, et al: Preoperative treatment of acromegaly with long-acting somatostatin analog 201-995: Shrinkage of invasive pituitary macroadenomas and improved surgical remission rate. J Clin Endocrinol Metab 67:1040-1048, 1988
8. Lamberts SWJ, del Pozo E: Somatostatin analogue treatment of acromegaly: New aspects. Horm Res 29:112-114, 1988
9. Besser GM, Wass JAH: Somatostatin octapeptide analogue (octreotide) in the medical management of acromegaly. Adv Biosc 69:221-225, 1988
10. Heron I, Thomas F, Dero M, et al: Pharmacokinetics and efficacy of a long-acting formulation of the new somatostatin analogue BIM 23014 in patients with acromegaly. J Clin Endocrinol 73:721-727, 1993
11. Melmed S: Acromegaly. N Engl J Med 322:966-977, 1990
12. Sassolas G, Harris AG, James-Dieder A, et al: Long term effect of incremental doses of the somatostatin analog SMS 201-995 in 58 acromegalic patients. J Endocrinol Metab 671:391-397, 1990
13. Vance ML, Harris AG: Long term treatment of 189 acromegalic patients with the somatostatin analogue octreotide. Results of the International Multicenter Acromegaly Study Group. Arch Intern Med 151:1573-1578, 1991
14. Diamanti E, Malachtari S, Thomas F, et al: Efficacy of a slow release formulation of the new somatostatin analogue lanreotide in acromegaly. The Endocrine Society, Las Vegas, NV, 1993, p 68 (abstr 72)
15. Kuhn JM, Basin C, Mollard M, et al: Pharmacokinetic study and effects of growth hormone secretion in healthy volunteers of the new somatostatin analogue BIM 23014. Eur J Clin Pharmacol 45:73-77, 1995
16. Tolis G, Koufopoulos S, Caldeimidis P, et al: Active acromegaly: Selective and non-selective effects of GH and insulin release by somatostatin receptor selective analogs and octreotide. The Endocrine Society, Washington, DC, 1995, p 498 (abstr P3-118)