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Reviews in Endocrinology: Optimizing the Management of Acromegaly in 2004

A Continuing Medical Education Enduring Material

Highlights of a Satellite Symposium held during the 86th Annual Meeting of The Endocrine Society

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Overview

There is continuing controversy within the endocrinology community on how to manage patients with acromegaly. An international panel of leading experts in the diagnosis and treatment of pituitary diseases recently participated in a symposium designed to help clinicians better manage acromegaly. Held during the 86th Annual Meeting of The Endocrine Society, the lectures were moderated by Michael C. Sheppard, MBChB, PhD, Professor of Medicine and Vice Dean at the University of Birmingham, UK, who also presented a section entitled, "Adjusting Therapy: What To Do When GH and IGF-1 Are Discordant." The other presenters were: Ilan Shimon, MD, of Sackler School of Medicine, Tel-Aviv University, Israel ("Preoperative Medical Therapy: What Can We Expect?"); Dr David L. Kleinberg from New York University School of Medicine, NY ("Primary Medical Therapy: Has the Time Come?"); and Dr Mark Molitch of The Feinberg School of Medicine, Northwestern University, Chicago, IL ("Should Tumor Shrinkage Be a Goal of Medical Therapy in Acromegaly?").

Introduction

Pierre Marie is credited with coining the term "acromegaly" circa 1886 to denote the consistently observed enlargement of the hands, feet, and face. While Massalongo proposed a causal relationship between an enlarged pituitary and acromegaly as early as 1892, it was not until Cushing noted the improvement after partial hypophysectomy in 1909 that the cause and effect relationship was confirmed.[1]

> "**Major advances** in surgical technique, radiation therapy, and new drug development have made acromegaly a disease that is now fully controllable."
>
> David A. Kleinberg, MD

Today, we acknowledge that acromegaly is a consequence of excessive growth hormone (GH) secretion. In turn, GH acts on peripheral tissue, primarily in the liver, to cause insulin growth factor-1 (IGF-1) release. The combination of elevated GH and IGF-1 results in bony expansion, dermatological changes, arthropathy, dental troubles, insulin resistance, and, most importantly, cardiovascular and pulmonary compromise.[2] These co-morbidities have been shown to decrease life-span by about 10 years in a New Zealand study[3] and increase the ratio of observed-to-expected deaths to 2.63.[4]

Most cases of acromegaly (about 98%) result from pituitary adenomas. Sixty percent of these are pure somatotropinomas and mixed tumors that secrete both GH and prolactin (mammosomatotropes) account for about 25%; other types of plurihormonal tumors that also produce TSH or ACTH are rare. Although these adenomas may occur as part of familial syndromes linked to specific inherited gene abnormalities, most cases are spontaneously acquired. On extremely rare occasions, hypothalamic tumors or "ectopic" tumors, such as carcinoids or pancreatic islet cell tumors, will secrete sufficient growth hormone releasing hormone (GHRH) to cause acromegaly.[5]

No specific data regarding the incidence or prevalence of acromegaly in the US have been published. Estimates of an incidence of 3 per million and prevalence of 40-60 per million are in keeping with studies from England[6] and Sweden.[7] Using the most recent census data that places the population of the US at 300 million, there are currently 12,000-18,000 Americans with acromegaly, and 900 new cases diagnosed each year. Due to the subtlety of the symptoms and the often-slow progression of the disease, it may take years to make the clinical diagnosis. For that reason, the aforementioned statistics probably underestimate the disease.

The development of more sensitive assays, coupled with a better understanding of the association between elevated GH levels and increased mortality in acromegalic patients, has increased the need for more effective biochemical cures. Although surgery remains the treatment of choice, the role of pharmocotherapeutic agents has expanded in light of the benefits of tighter biochemical control. The next 2 sections will explore the increased role of medical therapy in the treatment of acromegaly. The third section will examine whether tumor shrinkage should be a goal of therapy and the last will instruct the clinician as to the options available when GH and IGF-1 results do not agree.

Prepared under the auspices of The Endocrine Society.

Statement of Need

Acromegaly is a condition caused when the pituitary gland produces excess growth hormones. This condition causes excessive growth—occurring first in the hands and feet, and then extending to soft tissue. If left untreated, the disease can lead to severe illness and death.

According to the National Institute of Diabetes & Digestive & Kidney Disease (NIDDK), scientists estimate that about 3 of every million people develop acromegaly each year, and that 40 to 60 of every million people suffer from the disease at any time. However, these estimated figures are probably low, due to the subtlety of the symptoms, and the fact that the clinical diagnosis of acromegaly often takes years to make.

Once a diagnosis is established, there are various therapeutic pathways the endocrinologist may use to treat the patient.

In order to manage patients appropriately, physicians need a complete understanding of the efficacy and safety profiles of various treatment regimens. With this in mind, it is necessary to provide physicians with pertinent, up-to-date information regarding new advances in the diagnosis and management patients with acromegaly.

Educational Goal

A review of recent literature suggests differing opinions among endocrinologists on the management of acromegaly. The controversies include whether preoperative medical therapy is beneficial; the place of primary medical therapy in the treatment paradigm; and the use of GH and IGF-1 in the short-term and long-term monitoring of the effects of treatment. This CME Enduring Material will allow clinicians to compare their treatment practices with those of their peers, and learn the most current diagnostic and therapeutic recommendations.

Learning Objectives

At the conclusion of this activity, participants will be better able to:

- Examine the potential role of medical therapy in the perioperative setting for patients with acromegaly;
- Evaluate existing data regarding the use of primary medical therapy in the treatment of acromegaly;
- Describe the role of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in the development and manifestation of acromegaly;
- Evaluate data regarding tumor shrinkage with medical therapy; and
- Develop patient management strategies for cases in which results for GH and IGF-1 are discordant

Target Audience

This CME activity has been developed to meet the educational needs of clinical endocrinologists who manage patients with acromegaly.

Accreditation

The Endocrine Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The Endocrine Society designates this educational activity for a maximum of one category-1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This CME activity was planned and produced in accordance with the ACCME Essentials.

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Michael C. Sheppard, MBChB, PhD—Dr Sheppard has received research/funding support from Novartis Pharmaceuticals and IPSEN Pharmaceuticals. His presentation will not include a discussion of investigational or unlabeled use(s) of a product.

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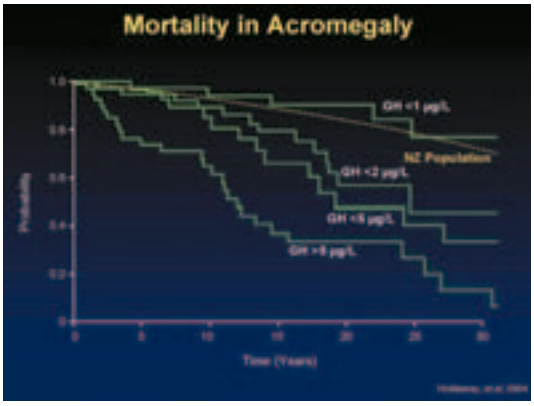
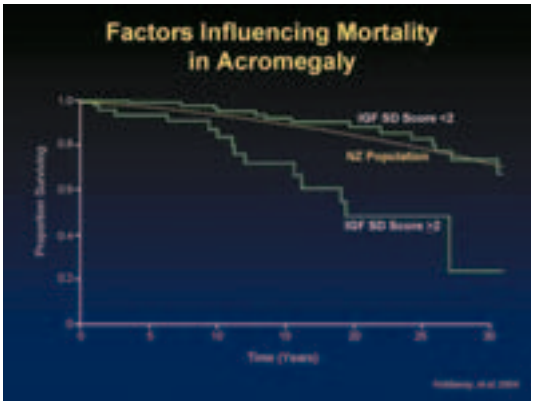




Highlights

Dr Sheppard commenced the final lecture of the symposium by conceding that assessment of disease activity in acromegaly following treatment is problematic because there is no established, specific endpoint that defines cure. The problem is compounded by the limitations and variability of the available assays for GH and IGF-1. Therefore, it is of critical importance that the physician becomes well acquainted with the type of assay being used by the referring laboratory and what "normal" means.

He noted that despite the fact that most epidemiological studies have related GH values, and not IGF-1 values, to long-term morbidity and mortality, there is a general consensus that control of disease has been achieved when mean GH levels are less than 2.5 mcg/L, nadir GH after an oral glucose load is less than 1 mcg/L, and IGF-1 is reduced to an age-adjusted normal range.

Studies by Swearingen et al[37] and Holdaway et al[38] support the use of IGF-1 as an indicator of mortality. Swearingen et al evaluated 162 patients treated with surgery and examined the relationship between normal postoperative IGF-1 values and mortality. Of the 57% that were considered "cured," 82% had normal IGF-1 levels. There was no significant difference in survival between these individuals with normal IGF-1 and controls. In contrast, patients with persistently elevated IGF-1 had an elevated mortality rate (SMR=1.18).

The first 2 graphs to the left summarize the study of Holdaway et al of a New Zealand cohort.

The first demonstrates the effects of GH. With reduction to less than 1 mcg/L, survival is similar to the general population. As GH levels increase (<2, <5, >5), survival rates decrease proportionately. The second demonstrates that normal IGF-1 values carry no increase in mortality rate, but elevations decrease survival starting at year 10. IGF-1 values are expressed as standard deviations from the mean to account for dissimilar values as a result of using different assays over the years.

In contrast, The West Midlands, UK, acromegaly study[39] did not find the same IGF-1 correlation. A total of 419 patients were enrolled and followed for a period ranging from 0.5 to 48 years. During the study, 95 patients died and IGF-1 data was available on 360 (86%). Some salient facts are illustrated in the tables below.

Clearly, acromegaly is associated with an increase in mortality rate over the expected (SMR*=1.28 p=0.046). When lowest GH values were greater than 2 mcg/L, there was an increased SMR of 1.31 (p=0.05). When lowest GH level was less than 2 mcg/L, there was an increased SMR of 1.10, but this was not statistically significant. When the effect of IGF-1 levels on mortality was examined, there was no statistically significant increase in mortality associated with elevation of IGF-1.

All Cause and Cause-specific Mortality in Acromegaly

Cause Mortality	Observed Deaths	Expected Deaths	SMR (95% CI)	P-value
All Cause	95	75.5	1.26 (1.03-1.54)	0.046
Cerebrovascular	20	7.5	2.68 (1.73-4.15)	0.007
Cardiovascular	35	25.6	1.37 (0.96-1.90)	0.111
Respiratory	13	8.6	1.52 (0.88-2.61)	0.219
Malignancy	21	23.1	0.91 (0.59-1.30)	0.650

Impact of GH Reduction, IGF-1 Normalization and Treatment With Radiotherapy on Mortality

Group	Observed Deaths	Expected Deaths	SMR (95% CI)	P-value
Lowest GH<2 µg/L	27	24.19	1.10 (0.76-1.63)	P=NS
Lowest GH>2 µg/L	67	51.2	1.31 (1.03-1.68)	P=0.05
IGF-1 Normal	32	30.3	1.05 (0.74-1.48)	P=NS
IGF-1 Elevated	29	27.2	1.07 (0.74-1.54)	P=NS
Radiotherapy	59	37.4	1.58 (1.22-2.04)	P<0.005
No Radiotherapy	36	38	0.95 (0.68-1.31)	P=NS

Experience has shown that GH and IGF-1 values do not always agree. In fact, they can be expected to be discordant in 20-30% of patients. With concordant normal values, there is no doubt that treatment is not required. Likewise, with concordant abnormal values, there is no disagreement that treatment is required. When GH is normal and IGF-1 is elevated, the general opinion of most clinicians is that treatment should be initiated. However, the paucity of clear evidence and the possibly contradictory results from the West Midland Study demonstrate that further research is needed before this recommendation can be made with certainty. When GH is elevated to >1mcg/L and IGF-1 is normal, treatment is probably indicated.

In conclusion, Dr Sheppard suggested that as GH assay sensitivity improves, perhaps the treatment goals would decrease to lower GH levels than are currently recommended. Freda et al[40] investigated the possibility of recurrence of disease in previously treated and cured patients. One hundred ten postoperative acromegaly patients were identified, 76 with normal IGF-1. Of these 76, one group (50 patients) had a nadir GH of <0.14mcg/L while another (26 patients) had values >0.14 but <1.0 mcg/L. Longitudinal follow-up of these 2 groups for 1-6.5 years revealed that in the group with GH<0.14, there was no new elevation of IGF-1. However, in the other group, there was a new elevation in 5 of the 26 patients, suggesting a recurrence.

Lastly, much like the previous presenters, he stressed the importance of not just treating the biochemical parameters. It is critical to also control the potentially life-threatening co-morbidities of acromegaly such as hypertension, cardiac failure, diabetes, respiratory distress, sleep apnea, and hypopituitarism.

*Standardized Mortality Ratio

Preoperative Medical Therapy: What Can We Expect?

Ilan Shimon, MD
Sheba Medical Center, Tel-Hashomer
Sackler School of Medicine
Tel-Aviv University, Israel

Ilan Shimon, MD, received his medical degree from Hadassah Medical School at Hebrew University, Jerusalem, Israel. He completed his residency in internal medicine in 1993 and a fellowship in endocrinology in 1994 at Sheba Medical Center, Tel-Hashomer, Israel. From 1994 to 1997, Dr Shimon served as a Post-Doctoral Fellow, Division of Endocrinology and Metabolism at Cedars-Sinai Medical Center, UCLA School of Medicine in Los Angeles, Calif. Since 1997, Dr Shimon has been a Senior Physician at the Institute of Endocrinology at Sheba Medical Center.

Dr Shimon has been the recipient of several honors and awards since 1994, including The Endocrine Society Merck Senior Fellow Award. Presently, he is the Secretary of the Israel Endocrine Society and Senior Lecturer in Medicine at the Sackler School of Medicine, Tel-Aviv University.

Dr Shimon has written or co-written more than 60 peer-reviewed publications and book chapters. Funded by a grant from the USA-Israel Binational Science Foundation, Dr Shimon's current research is focused on growth hormone regulation and adhesion molecules.

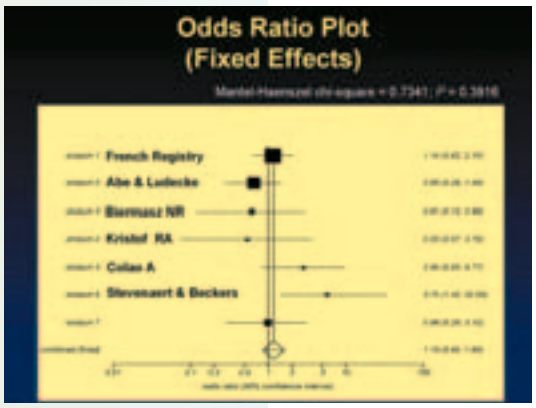
Highlights

Dr Shimon believes that possible benefits of preoperative medical therapy with somatostatin analogs include decreasing tumor size, improving visual deficits, decreasing the risk of hypopituitarism, improving postoperative remission rate, and decreasing perioperative morbidity.

He presented work by Amato et al[8] in which treatment of both micro- and macro-adenomas with octreotide LAR or lanreotide SR (not currently approved in the US) resulted in significant tumor shrinkage. Most of the effects were noted during the first 12 months of therapy. Since it takes time to see this shrinkage, it was the opinion of the presenter that surgical intervention is the treatment of choice when visual impairment is noted. In cases where surgery is unable to remove the tumor completely, somatostatin analogs may be considered to shrink the tumor.

Pre-surgical Treatment (292)
Untreated (339)
Summary of 6 Publications

	Surgical Remission Rate			
	Pre-treated		Untreated	
	No.	%	No.	%
All	292	63.4	339	54.5
Non-invasive	166	83.7	169	74



A literature review to determine if preoperative medical therapy improved surgical outcome revealed only 6 comparative studies. These were not randomized, placebo-controlled. In addition, most studies reported retrospective analysis, they used only short-acting analogs; selection bias was involved; there was no consistency in dosage or treatment interval; and no studies used dopamine agonist or GH receptor antagonist. A summary of 6 publications appears to the left.

Although remission rates were mildly improved with preoperative somatostatin analog treatment, an odds ratio plot of the data shows that improvement was not statistically significant. [9-14]

Increased perioperative risks in acromegaly result from cardio-respiratory morbidities, including left ventricular hypertrophy (LVH); reduced left ventricular ejection fraction (LVEF); hypertension; increased risk of cerebrovascular disease; swelling of the upper respiratory tract resulting in obstruction and more difficult intubations; sleep apnea; and diabetes mellitus.

Colao et al[15] reported that treatment with octreotide reduces LVH and improves LVEF. Ip et al[16] noted a correlation of baseline GH with tongue length and sleep apnea. After treatment with octreotide, both apnea-hypopnea and obstructive-apnea indexes improved. Lastly, Seidman et al[17] compared 28 patients with acromegaly to 28 matched non-acromegalic patients undergoing pituitary transsphenoidal surgery, and noted more airway difficulties (12 vs. 1) in acromegaly.

In summary, Dr Shimon concluded that somatostatin analogs were of benefit in treating the cardiorespiratory morbidities of acromegaly in the preoperative stage. Although there is evidence to suggest that preoperative therapy with somatastatin analogs may improve surgical outcome, there are no statistically significant data to support its use. A large, prospective multi-center, randomized placebo-controlled study is needed.

Primary Medical Therapy: Has The Time Come?

David L. Kleinberg, MD
New York University Medical Center
New York, NY

David L. Kleinberg, MD, is Professor of Medicine and Director of the Neuroendocrine Unit at New York University School of Medicine, New York, NY, and consultant at the Veterans Affairs, New York Harbor Health Care System, NY. He is an attending physician in the Department of Medicine at New York University Medical Center and at Bellevue Hospital in New York. Dr Kleinberg is the President of The Pituitary Society and has served on the editorial board for the *Journal of Clinical Endocrinology and Metabolism* and is currently on the editorial board of *The Pituitary*. He co-authored the anterior pituitary chapter in the 10th Edition of *Williams Textbook of Endocrinology* and authored the chapter on Mammary Development, Lactation, and Galactorrhea in the fourth edition of *Endocrinology* (DeGroot and Jameson, eds). Both public and private institutions, including the NIH, fund his research on the effects of GH and IGF-1 on mammary and prostate development.

Dr Kleinberg was one of several investigators who showed that prolactin and growth hormone were separate molecules in human beings. The bioassay for prolactin that he co-developed was capable of detecting serum prolactin at 15 ng/mL. It enabled him and his colleagues to recognize how common hyperprolactinemia was as a clinical problem, and that prolactin was elevated in patients with pituitary tumors and galactorrhea. His article on the pathophysiology of galactorrhea remains the standard work on that subject, and one of the most frequently cited. He is a recognized authority on growth hormone deficiency and the treatment of acromegaly and other pituitary tumors. He has authored numerous peer-reviewed papers in the field of clinical and experimental endocrinology.

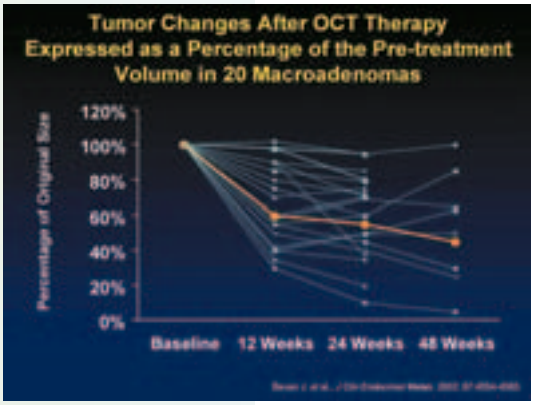
Dr Kleinberg and his colleagues have forged new ground in the understanding of the hormonal control of mammary and, recently, prostate development. He determined that growth hormone through the action of locally produced IGF-1 in the mammary gland was essential to pubertal mammary development, and that estrogen had no effect on mammary development in the absence of IGF-1. IGF-1 is also essential for prostate development. Recently he has focused his clinical research on the effects of aging on growth hormone dynamics and IGF-1, and also on developing new treatment paradigms for acromegaly.

Effect of Somatostatin Analogs as Primary Therapy

Drug	Author	# Pts	GH <2.5 %	NI IGF-1 %	% Shrunk
Oct SC (LAR)	Bevan	27	38	33	100
LAR	Cozzi	51	66-93	69-80	76.7
LAR	Colao	15	69.4	61.1	60
Lanreo	Lucas	104	NA	NA	66 (29)
Lanreo	Baldelli	23	78	70	22
MEAN		220	68.4	62.4	67.6

Details of Tumor Shrinkage

Author	Drug	Supplicant Shrinkage %	Median Tumor Volume Reduction	% Shrunk
Bevan	OCT	>12 >6	49% micro 43% macro	100
Cozzi	OCT	>25	–	76.7
Colao	OCT	>25	–	60
Lucas	LAN	>20	–	29
Baldelli	LAN	>20	–	22



Highlights

According to Dr Kleinberg, the principal goals in the treatment of acromegaly are: control of GH to less than 1 mcg/L during an oral glucose tolerance test; removal, reduction or control of tumor mass; reduction of IGF-1 levels to age and gender matched normal levels; and preservation of pituitary function. Achieving these goals by aggressively managing the co-morbidities associated with acromegaly will prevent early deaths.

Since somatostatin analogs are able to achieve the goals of therapy without the inherent risks of surgery, primary medical therapy using these agents has received consideration. Surgical intervention in the hands of experienced, neurosurgical teams has demonstrated a cure rate of 70-90% for small, non-invasive adenomas. In contrast, only 20-50% of larger, invasive tumors can be expected to be cured.[18]

In 1998, Newman et al[19] showed that GH and IGF-1 could be reduced with short-acting octreotide in both previously treated (surgery and/or radiation) and never treated patients.

Summation of data from 5 separate studies by Bevan et al,[20] Cozzi et al,[21] Colao et al,[22] Baldelli et al,[23] and Lucas et al[24] using long-acting somatostatin analogs appears to the left.

GH, IGF-1, and tumor size were all reduced in a significant number of patients. Most tumor shrinkage occurred within the first 12-24 weeks of therapy.[20]

Dr Kleinberg's "New York View" is that, given the high cure rate in the hands of capable surgeons, small non-invasive tumors will likely do better with surgery. Primary medical therapy with a somatostatin analog is a reasonable option for larger or invasive tumors that are not likely to be cured by surgery alone. A prospective, randomized study on whether debulking non-threatening macroadenomas improves the outcome of medical therapy is needed to determine if surgery plus somatostatin agonist is superior to medication alone.

Pegvisomant is a growth hormone receptor antagonist that has been shown to be effective in the treatment of acromegaly. This medication was not included in the consideration for primary medical therapy, as not enough data are currently available.

Should Tumor Shrinkage Be a Goal of Medical Therapy in Acromegaly?

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Mark E. Molitch, MD, is Professor of Medicine and a Member of the Division of Endocrinology, Metabolism and Molecular Medicine at Northwestern University Feinberg School of Medicine, in Chicago, Ill. Prior to joining the faculty at Northwestern in 1984, Dr Molitch was an Associate Professor at Tufts University School of Medicine in Boston, Mass.

Dr Molitch earned an BA degree from Princeton University and an MD from the University of Pennsylvania. He did his housestaff training at the Hospital of the University of Pennsylvania and received an Endocrine Fellowship at the UCLA-Harbor General Hospital in Torrance, Calif.

Dr Molitch has participated in clinical research for many years, focusing on the pathogenesis of pituitary tumors as well as their treatment. He has been involved in most of the initial trials of therapeutic agents for pituitary tumors, including those using bromocriptine, mesulergine, quinagolide, cabergoline, octreotide, octreotide-LAR, and lanreotide. He has also participated in international diabetes trials, including the Diabetes Control and Complications Trial, the Diabetes Prevention Program and the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial.

In addition to editing 6 books, Dr Molitch has authored or co-authored more than 250 original papers, review articles, book chapters, case reports, and other publications. Dr Molitch is currently an Associate Editor of the *Year Book of Endocrinology* and an Editor of the journal, *Pituitary*. In 1997, Dr Molitch was named "Outstanding Physician Educator in the Field of Diabetes" by the American Diabetes Association.

Highlights

Dr Molitch began his presentation with a review of the available medical therapies for acromegaly: dopamine agonists bromocriptine and cabergoline, somatostatin analogs octreotide and lanreotide, and GH receptor antagonist pegvisomant.

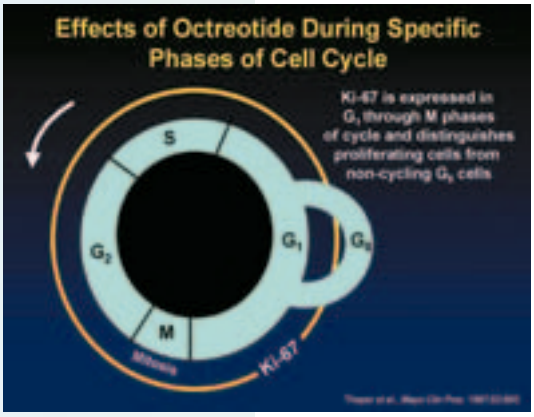
Bromocriptine has been shown to effectively reduce GH and IGF-1 in only 10% of cases, with negligible effects on tumor size.[25] In 2 series, cabergoline was able to normalize IGF-1 in about 33% of patients and reduce tumor volume in 43% of patients when used as an adjunct following surgery or radiation.[26, 27] However, in another group of 11 patients, the author was unable to document any cases with normalization of IGF-1 or tumor reduction.[28]

Although pegvisomant has been shown to normalize IGF-1 levels in 97% of patients (n=90), it has no direct effect on the tumor.[29] Tumor enlargement seen during its use may be due to the natural history of the tumor or the loss of negative IGF-1 feedback. GH values were noted to increase as a result of pegvisomant therapy.[30]

The greatest experience is with somatostatin analogs which can cause a normalization of GH and IGF-1 in 50-60% of patients.[31] Tumor shrinkage is also common with somatostatin analogs. Data compiled by Dr Molitch from approximately 20 studies for presentation at this symposium show that with primary therapy, tumor shrinkage occurred in 42.7% of 328 patients treated with subcutaneous (SQ) octreotide;76.2% of 101 patients treated with octreotide-LAR; and 23% of 200 treated with SQ lanreotide. When used as adjunctive therapy, the numbers were: 35.4% of 302 patients treated with subcutaneous (SQ) octreotide; 29.6% of 98 patients treated with octreotide-LAR; and 19.6% of 184 treated with SQ lanreotide.

In the aforementioned series, tumor enlargement while on somatostatin therapy was only noted in 29 of 1213 patients (2.4%). Interestingly, 19 came from a single paper involving 104 patients treated with lanreotide. The possibility of tumor growth after cessation of treatment with somatostatin analogs was addressed by Ezzat et al[32] in a multicenter study. Of the patients that responded with tumor shrinkage to octreotide (20 of 70), 20% experienced tumor re-expansion. No expansion beyond the original size was observed.

Numerous authors have investigated the relationship between reduction in tumor size and hormonal parameters.[19,20,22,31,33] No correlation could be established between the percentage of somatostatin-induced tumor mass reduction and the percentage of GH and IGF-1 reduction.



The mechanism by which somatostatin analogs reduce tumor size or suppress further growth is not completely understood. Histological changes are variable and do not consistently reveal cell necrosis.[34]

The illustration to the left depicts a cell cycle. Of importance is the fact that the nuclear antigen Ki-67 is only expressed in G1 to M and not by non-cycling G0 cells. After 4 months of treatment with octreotide, the mean growth fraction, as defined by the presence of labeled Ki-67, was suppressed by 83% compared to untreated controls.[35]

Although a reduction in Ki-67 labeling index signifies a reduction of the proportion of cell in G1 to M, it does not indicate where octreotide exerts its antiproliferative effect. A study by Losa et al[36] sought a possible correlation between antiproliferation and changes in tumor size. They noted that Ki-67 labeling index was not only lower in treated versus not treated patients, but that it was lower in tumors that decreased in size compared to tumors whose size did not change ($p<0.02$). However, there was no change in the apoptotic index. More research is needed.

In conclusion, Dr Molitch noted that control of tumor growth should be an explicit goal of medical therapy of acromegaly and that somatostatin analogs are the agents most likely to affect control of tumor growth. He agreed with Dr Kleinberg that in patients who are unlikely to be cured by surgery, somatostatin analogs might provide a useful, effective alternative. Lastly, he noted that many of the studies cited were not optimal (patients were pre-selected, details of tumor size reduction were omitted) and that there are no prospective, randomized comparisons of somatostatin analogs to either dopamine analogs or pegvisomant with respects to either tumor size or IGF-1 levels.

"...assessment of disease activity in acromegaly following treatment is problematic because there is no established, specific endpoint that defines cure."

Michael C. Sheppard MBChB, PhD

Adjusting Therapy: What To Do When GH and IGF-1 Are Discordant

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Michael C. Sheppard, MBChB, PhD, is Vice Dean of the University of Birmingham (UK) Medical School and Head of the Department of Medicine. Dr Sheppard is a member of the Executive Committee of the European Federation of Endocrine Societies and Chairman of the Programme Organizing Committee for the European Congress of Endocrinology in 2005.

In addition to these duties, Dr Sheppard is the Clinical Committee Chair of the Society for Endocrinology UK and former President of the Royal Society of Medicine, Endocrine Section. He has co-authored close to 60 research articles in the last 6 years alone, published in such prestigious medical journals as *New England Journal of Medicine, Lancet, Journal of Clinical Endocrinology and Metabolism, Clinical Endocrinology* and *Archives of Internal Medicine.* He was Chairman of the SAC in Endocrinology and Diabetes of the Royal College of Physicians.

Dr Sheppard's research interests focus on the epidemiology and management of pituitary disease, pituitary tumor pathogenesis, outcome of thyrotoxicosis, and management of thyroid cancer. Dr Sheppard's most current research focuses on better understanding of pituitary tumor development and innovative acromegaly therapies.

Dr Sheppard's clinical interests focus on pituitary and thyroid disease diagnosis and management, as well as general endocrinology. He presents his research and delivers lectures regularly at such worldwide conferences as the 6th European Congress of Endocrinology, the German Endocrine Society, the British Endocrine Societies' Annual Meeting, the Mexican National Congress of Endocrinology, the European Neuroendocrine Association, and the US Endocrine Society Annual Meeting. Dr Sheppard was also recently a visiting Professor of Endocrinology at both Cedars-Sinai Research Institute (University of California at Los Angeles) and Massachusetts General Hospital (Boston).

Dr Sheppard completed his PhD in 1979 at University of Cape Town, South Africa, and was elected a Fellow of the Royal College of Physicians in 1985 and Founder Fellow of the Academy of Medical Sciences in 1998. He became a Professor of Medicine at the University of Birmingham in 1986 and head of the University's Department of Medicine in 1992. Dr Sheppard was honored by being named William Withering Professor of Medicine in 2000. He currently resides in Birmingham, UK.

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The completed posttest answer grid and evaluation form should be faxed to 301-941-0259 or mailed to: The Endocrine Society, Attention CMES, 8401 Connecticut Avenue, Suite 900, Chevy Chase, MD 20815.

Self-Assessment Posttest

After reading the text, choose the correct answer for each question, and circle the answer on the answer grid. You must answer at least 70% of the questions correctly to receive credit.

1. **Which of the following statements regarding the treatment of recurrent acromegaly is correct?**
   - **A.** Treatment should be considered only when GH is elevated
   - **B.** Treatment should be considered only when IGF-1 is elevated
   - **C.** Treatment should be considered when either GH or IGF-1 is elevated
   - **D.** Treatment should be considered only when both GH and IGF-1 are elevated

2. **Important co-morbidities of acromegaly that require aggressive management include:**
   - **A.** Diabetes mellitus
   - **B.** Hypertension
   - **C.** Decreased cardiac output
   - **D.** All of the above

3. **When using somatostatin analogs in the treatment of pituitary adenomas, most tumor shrinkage was noted:**
   - **A.** During the first 6 months of treatment
   - **B.** During months 6-12 of treatment
   - **C.** During months 12-24 of treatment
   - **D.** After 24 months of treatment

4. **Which statement regarding the epidemiology of acromegaly is correct?**
   - **A.** The estimated incidence is about 6-10 per million
   - **B.** The estimated prevalence is about 40-60 per million
   - **C.** Current estimates suggest that there are 5,000 Americans with acromegaly

5. **In the hands of experienced neurosurgical teams, operative cure rates for microadenomas versus macroadenomas are:**
   - **A.** 70-90% versus 20-30%
   - **B.** <50% versus 20-30%
   - **C.** 70-90% versus 40-50%
   - **D.** About the same

6. **The class of agent most likely to effect tumor growth is:**
   - **A.** Dopamine agonists
   - **B.** GH receptor antagonists
   - **C.** Somatostatin analogues

7. **Goals for treatment of acromegaly should include:**
   - **A.** Control of GH to less than 1 mcg/L
   - **B.** Control of IGF-1 to age and gender matched levels
   - **C.** Control of tumor mass
   - **D.** All of the above

8. **Possible benefits of preoperative medical therapy with somatostatin analogs include:**
   - **A.** Improving remission rate
   - **B.** Decreasing tumor mass
   - **C.** Decreasing the risk of hypopituitarism
   - **D.** All of the above

9. **Correct statements regarding the relationship between tumor size and hormonal parameter include:**
   - **A.** A linear correlation exists between tumor mass reduction and percentage of GH reduction
   - **B.** A linear correlation exists between tumor mass reduction and percentage of IGF-1 reduction
   - **C.** No linear correlation exists between tumor mass reduction and percentage of GH or IGF-1 reduction

10. **Which of the following statements is incorrect?**
    - **A.** About 60% of GH-producing pituitary tumors are pure somatotropinomas
    - **B.** About 25% of GH-producing tumors also produce TSH
    - **C.** Carcinoid tumors may cause acromegaly
    - **D.** Pancreatic islet cell tumors may cause acromegaly

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Answer Grid (Circle the correct answer.)

1	2	3	4	5	6	7	8	9	10
A	A	A	A	A	A	A	A	A	A
B	B	B	B	B	B	B	B	B	B
C	C	C	C	C	C	C	C	C	C
D	D	D		D		D	D		D

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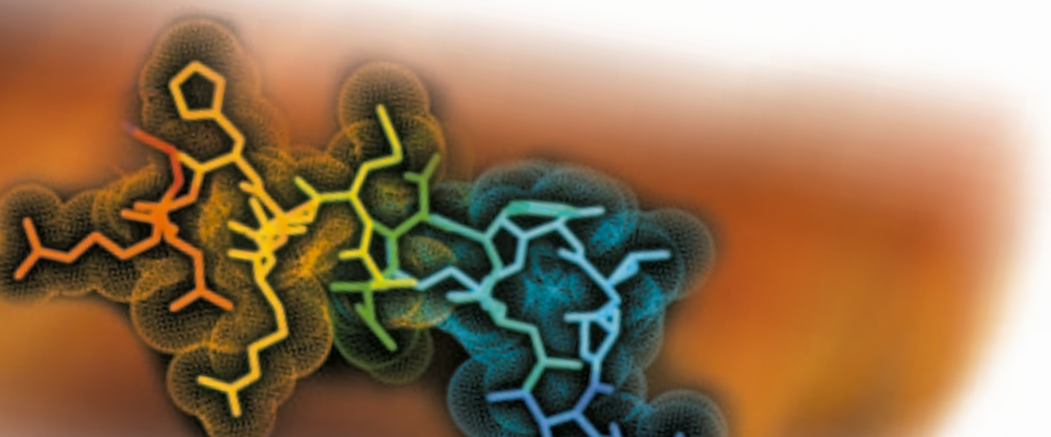
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