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HOT TOPICS IN NEUROENDOCRINE RESEARCH:

Investigational Uses of Recombinant Human Growth Hormone: Focus On Obesity and Congestive Heart Failure

Nicholas A. Tritos, M.D., D.Sc.

Introduction

Since 1985 the increased availability of growth hormone preparations in recombinant form (rhGH) has led to studies of its efficacy and safety in conditions beyond classic growth hormone deficiency (GHD) in childhood. In addition to its widely investigated role as replacement therapy in patients with deficient growth hormone (GH) secretion as a result of pituitary disease or idiopathic childhood-onset GH deficiency, rhGH has been found to be efficacious in several conditions associated with resistance to endogenous GH (1,2). Several lines of evidence have led to the establishment of an expanding number of FDA approved indications for rhGH therapy as shown in Table 1 (such as pediatric chronic renal failure, Turner & Noonan syndrome, adult HIV wasting and short bowel syndrome). The effects of rhGH administration have also been examined in a wide variety of disease states thought to be associated with either relatively deficient GH secretion or action. This review will summarize available information on the effects of rhGH in two such diseases in adults: obesity and congestive heart failure. It should be emphasized that the use of rhGH in these conditions remains investigational and should not be pursued outside of well-designed clinical trials at the present time.

Obesity

Obesity has become increasingly prevalent in western countries in the past three decades (3). Currently, two-thirds of adults in the US are either obese or overweight. Obesity has been associated with substantial increase in morbidity and mortality, accounting for up to 300,000 deaths annually in the US alone. It has been suggested that the dramatic rise in the prevalence of obesity may lead to a decline in life expectancy in the 21st century (4). There is an unmet medical need for highly efficacious and safe non-surgical therapies for obesity, which has led to the investigation of several potential agents, including rhGH.

Obesity has been associated with a decline in spontaneous as well as evoked GH secretion (5,6). Frequently sampled serum GH levels indicate that endogenous GH secretion is blunted in obesity and is restored by weight loss. In addition, increased body adiposity is associated with a decline in GH secretion in response to a variety of evocative stimuli, including insulin-induced hypoglycemia and growth hormone releasing hormone (GHRH) - arginine. Neither the cause nor the pathophysiologic consequences of impaired GH secretion in obesity have been clearly elucidated. There are well-established lipolytic and protein-sparing (anabolic) effects of rhGH in animal models, and the beneficial effects of rhGH administration in GHD adults with pituitary disease include improvement in body adiposity and bone density, systemic lipid profile, and cardiovascular function. These findings have spurred interest in the potential role of rhGH as a therapy in simple, non-syndromic obesity in adults [which is not associated with classic endocrinopathies or human immunodeficiency virus (HIV) associated lipodystrophy] (7).

Several studies have examined the effects of rhGH administration in obesity. However, most studies have been relatively small in size or of short duration, and have

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Table 1 **FDA approved indications for rhGH therapy.**

Growth failure in children with	Adults with
Growth hormone deficiency (idiopathic or as a result of pituitary disease)	Growth hormone deficiency as a result of pituitary disease or childhood-onset GHD
Chronic renal failure	HIV infection–associated cachexia
Turner syndrome	Short bowel syndrome
Prader Willi syndrome	
Intrauterine growth retardation (small for gestational age)	
Idiopathic short stature	
SHOX gene deficiency	
Noonan syndrome	

Table 2 Results of a meta-analysis of the effects of rhGH administration on laboratory endpoints in obesity.

Endpoint	Weighted mean difference	95% CI	P value	No. of studies	No. of subjects (GH)	No. of subjects (placebo)	Total no. of subjects	Q test P value	I^2 index (%)	Global effect size
IGF-I (μg/liter)	171	131–212	<0.001	20	204	206	410	<0.001	85	
Leptin (μg/liter)	−1.8	−4.1–0.5	0.130	4	57	51	108	0.477	0	
TC (mg/dl)	−7	−11 to −3	0.001	13	164	153	317	0.379	7	
LDL-cholesterol (mg/dl)	−9	−13 to −5	<0.001	9	130	119	249	0.244	22	
HDL-cholesterol (mg/dl)	−0.4	−3–2	0.779	11	139	124	263	0.105	37	
TG (mg/dl)	1	−9–11	0.811	14	177	168	345	0.281	16	
Lp(a) (g/liter)	0.02	−0.03–0.07	0.330	3	43	46	89	0.707	0	
FPG (mg/dl)	3	1–6	0.004	16	166	158	324	0.002	57	
Insulin (μU/ml)	1.9	0.2–3.7	0.037	14	146	140	286	<0.001	76	
HbA1$_c$ (%)	−0.1	−0.2–0.03	0.125	5	69	60	129	0.922	0	
HOMA-IR	−0.6	−1.6–0.4	0.236	3	54	44	98	0.124	52	

TC, total cholesterol; TG, (serum) triglycerides. SI unit conversion factors are as follows: for IGF-I, 0.13 × μg/liter = nmol/liter; cholesterol, 0.026 × mg/dl = mmol/liter; triglycerides, 0.011 × mg/dl = mmol/liter; glucose, 0.055 × mg/dl = mmol/liter; insulin, 7.175 × μU/ml = pmol/liter.

From Mekala et al. J Clin Endocrinol Metab. 2009; 94(1):130-7. (11) *Copyright 2009, The Endocrine Society.*

led to conflicting results (8-10). A meta-analysis of 24 placebo-controlled studies of rhGH administration in simple obesity in adults has recently been published, and included 539 subjects, 477 of whom completed participation in individual studies (11). Inclusion criteria varied, with mean body mass index (BMI) ranging from 28 to 42 kg/m^2. There were ten studies that enrolled only women and four studies that included men only. Treatment with rhGH varied with regards to dose, which was frequently supraphysiologic, as well as duration (3-72 weeks).

Overall, there were no significant effects of rhGH on body weight and BMI in the entire study population examined. However, rhGH administration led to statistically significant benefits with regards to fat mass (mean decrease by 0.9 kg), percent body fat (mean decrease by 1%) and visceral adiposity (based on computerized tomography). There was a significant increase in lean body mass (mean of 1.8 kg). Changes in body composition were paralleled by beneficial effects in systemic lipid profile, including small but significant decreases in total and low density lipoprotein (LDL) cholesterol (Table 2).

Arthralgias, paresthesias (secondary to carpal tunnel syndrome) and fluid retention (peripheral edema) were significantly more frequent among subjects allocated rhGH than placebo (odds ratios 5-6.5). These findings are not surprising in view of the high rhGH doses used in many of these studies. There were also small, but significant increases in fasting plasma glucose (mean increase by 3 mg/dl) and fasting insulin (mean increase by 1.9 mcU/ml), as shown in Table 2. However, the latter finding was only present among studies of shorter duration (below the median duration of 11.5 weeks).

In aggregate, currently available data suggest that rhGH has a relevant role in influencing body composition and cardiovascular risk factors in obesity, even though it does not induce weight loss. At the present time, the benefits of rhGH administration in obesity appear to be small and the potential risks inadequately characterized. Future studies of longer duration, using carefully titrated rhGH therapy protocols designed to maintain normal serum insulin-like growth factor 1 (IGF-1) concentrations, are needed in order to establish the long-term risks and benefits of this therapy in obesity. In addition, GH secretagogues, including GHRH or ghrelin and its mimetics, may have a relevant, but currently unproven, role as therapeutic agents in obesity and could potentially be safer than rhGH, as negative feedback effects of endogenous GH remain intact in response to secretagogue administration.

Congestive heart failure

Congestive heart failure (CHF) currently affects approximately 5.7 million Americans and accounts for approximately 292,000 deaths per year in the US (12). Despite improvements in diagnosis and therapy, CHF remains a major contributing factor to morbidity and mortality, necessitating the development of novel therapeutic agents for this condition.

Data from experimental studies in animal CHF models have suggested a beneficial effect of GH administration (13). Both *in vitro* and *in vivo* studies demonstrated that GH administration may have positive cardiac inotropic effects, mediated through changes in myocardial gene expression and cardiac sarcoplasmic reticulum calcium channel activity, as well as systemic vasodilation (14). In humans with GHD due to pituitary disease, several studies have indicated beneficial effects of rhGH replacement on echocardiographic indices of cardiac function (15). It has also been suggested that patients with CHF, particularly those with cachexia, may have resistance to endogenous GH (16). These observations have stimulated interest in the potential role of rhGH therapy in adults with CHF due to systolic dysfunction.

Uncontrolled studies in patients with CHF showed beneficial effects of rhGH therapy on functional, echocardiographic and hemodynamic parameters (17). However, subsequently performed placebo-controlled studies showed little or no benefit (18). Two meta-analyses of studies involving rhGH administration in patients with CHF secondary to systolic dysfunction have been published, including 12 or 14 studies, and 195 or 212 patients, respectively (19,20). All patients had CHF secondary to systolic dysfunction [mean baseline New York Heart Association (NYHA) class ~ 2.5 and left ventricular ejection fraction ~ 25%]. Most of these studies were of short duration (2-3 months) and frequently involved supraphysiologic rhGH administration, in addition to standard therapies for CHF (angiotensin converting enzyme inhibitors, diuretics, beta adrenergic antagonists, digitalis and anticoagulants).

Findings from both meta-analyses suggested statistically significant improvements in exercise capacity (mean increase: 1.9 min) and maximal oxygen consumption during exercise, as well as improvements in NYHA class (mean change: -0.9). These findings were paralleled by positive hemodynamic effects (including an increase in cardiac output with a concurrent decrease in systemic vascular resistance) and improvements in ejection fraction on echocardiography. Despite increases in left ventricular mass and wall thickness, there were no adverse effects on diastolic heart function.

Safety monitoring showed no increase in death risk or CHF exacerbation among patients who received rhGH therapy in comparison with control subjects. However, there was an increased risk (~ 5% of patients) of ventricular arrhythmia among rhGH treated subjects, which was only present in one study. As this study was uncontrolled and included patients with severely decreased ejection fraction, it remains unclear whether rhGH administration was causally related to arrhythmogenesis. This finding requires further evaluation in future studies.

Overall, available data suggest that rhGH administration in patients with CHF secondary to systolic dysfunction appears to have positive effects on functional, hemodynamic and echocardiographic indices of cardiovascular function. However, there are no long-term data on the effects of rhGH on cardiovascular morbidity and mortality. In addition, there are significant concerns regarding the safety of this therapy that remain to be clarified. Future studies will need to use carefully titrated rhGH dosing regimens, aimed at maintaining normal serum IGF-1, in order to avoid the long-term adverse consequences of rhGH excess, and examine specific clinical endpoints before this therapy can be recommended. In addition, the therapeutic role of ghrelin, which has been reported to have beneficial effects in patients with CHF in preliminary studies, requires further investigation (21).

Summary

Our understanding of the role of the GH–IGF-1 axis in physiologic and pathophysiologic conditions continues to expand, facilitated by the availability of rhGH. Nevertheless, many questions remain incompletely answered regarding the therapeutic role of rhGH in conditions associated with a relative decline in endogenous GH secretion, including obesity, or resistance to endogenous GH, including CHF. Future well-designed, adequately powered, controlled clinical trials should help clarify the controversies regarding the potential therapeutic role of rhGH in these conditions. Until then, clinical use of rhGH therapy outside of well-designed controlled clinical trials should be restricted to FDA approved indications.

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The Neuroendocrine Clinical Center Welcomes Dr. Nicholas Tritos

Dr. Tritos received his training in Endocrinology at Beth Israel Deaconess Medical Center and held faculty appointments there and at Joslin Diabetes Center. He received a M.MSc. from Harvard Medical School. Since 2005, Dr. Tritos has been a full-time Senior Staff Physician at the Lahey Clinic. He was an Assistant Professor of Medicine at Tufts University School of Medicine, where he has been a member of the Curriculum Committee. At Massachusetts General Hospital, Dr.Tritos will be seeing patients with pituitary and neuroendocrine disorders full-time in the Neuroendocrine Clinical Center as well as consulting on inpatients, teaching and maintaining involvement in clinical research studies.

Update on Transsphenoidal Surgery for Cushing's Disease

Brooke Swearingen, M.D.

Although there have been recent advances in both the medical and radiosurgical management of Cushing's disease, transsphenoidal surgery remains the primary treatment for newly diagnosed cases. In order to answer a number of outstanding questions regarding the management of this disease, we reviewed 181 cases of Cushing's disease treated at MGH by a single neurosurgeon (B.S.) between the years of 1998-2006, with a median follow-up of five years (range 2-10). Criteria for cure were defined as subnormal post-operative 24 hour urine cortisol levels or fasting serum cortisol levels <5µg/dl.

1. How effective is transsphenoidal surgery in achieving remission?
The effectiveness of the procedure is a function of tumor size, invasiveness, and whether the patient has undergone previous treatment. In a newly diagnosed patient with a microadenoma, the overall surgical success rate at our institution was 91% (126/139). The surgical remission rate at the initial procedure was 83% (115/139). If the first procedure was unsuccessful, we generally recommended a second exploration to search for residual tumor. The second procedure was successful in 73% (11/15).The majority of patients with Cushing's disease have microadenomas. For patients with macroadenomas (>1cm), the success rate was lower, as expected, at 67% (12/18).

2. Does the presence of tumor seen on MRI correlate with surgical success?
In patients with microadenomas, tumor was visualized on MRI in 65% of cases. The remission rate if tumor was seen radiographically was 94% (84/89), and 84% if a tumor was not visible on MRI. This suggests that further improvements in surgical remission might be achieved with better radiographic visualization, perhaps with higher field strength MRIs.

3. Does confirming tumor presence on pathologic analysis correlate with remission?
In patients with microadenomas, tumor was confirmed pathologically 75% of the time. If tumor was found, the remission rate was 93% (98/105), as opposed to 82% (28/34) if it was not.

4. How can remission be achieved with negative pathology?
These tumors are so small that they often times do not survive the standard processing procedure required for pathological analysis. Because these tumors can be less than a mm in size, it is also possible that the tumor could be removed or destroyed during the microsurgical exploration even if no tumor is actually seen.

5. If a patient has had an unsuccessful procedure elsewhere, can remission be achieved with a second operation?
Twelve patients had previously unsuccessful procedures at outside institutions and were referred for re-exploration; eight of them (67%) were cured after a second procedure at MGH.

6. What is the complication rate?
The surgical mortality and incidence of new visual compromise or neurological deficit were zero. There were three cases of CSF rhinorrhea requiring surgical repair, and two cases of epistaxis which required nasal packing. Postoperative hormone replacement was initiated in approximately 14%, although some of these patients may have had pre-operative pituitary dysfunction. The incidence of postoperative prolonged diabetes insipidus was 1%.

7. What is the risk of recurrence?
Recurrence risk appears to be a function of tumor size. The recurrence rate for microadenomas was 11% at five years, while it was 33% for macroadenomas.

8. How should recurrences be managed?
Of the 14 patients with recurrent microadenomas, 12 underwent re-exploration, and 75% (9/12) achieved remission on re-exploration. Two of these later recurred again. Of the three patients with recurrent macroadenomas who underwent re-exploration, 2/3 achieved post-operative remission, although one had a later recurrence. These results will need to be compared with the remission data after proton radiosurgery, which remains a viable option in patients with recurrent disease. Fifty percent of patients treated with radiosurgery are in remission at 24 months after treatment, although 50% of the radiated patients are deficient in at least one hormone axis at that point as well. It is important to note that all forms of radiation therapy may lead to long-term decreased anterior pituitary hormone function.

In summary, transsphenoidal surgery when performed by an experienced pituitary surgeon remains a safe and effective treatment for Cushing's disease, with a high chance of success and low complication rate. Surgical success is a function of neurosurgical experience, tumor size and invasiveness and correlates with radiographic visualization and pathologic confirmation. Re-operation after initial failure is often successful, especially in patients with microadenomas. Treatment of recurrences needs to be individualized, but re-operation remains a useful option, along with radiosurgery and, possibly, new medical therapies.

JOURNAL CLUB

Potential Pituitary-directed Therapies for Cushing's Disease

Beverly M.K. Biller, M.D.

The January 2009 edition of *The Journal of Clinical Endocrinology and Metabolism* featured two original reports regarding potential medical treatments for Cushing's disease that directly target corticotroph adenoma cells. The treatment of choice for Cushing's disease (Cushing's syndrome due to a pituitary adenoma) is transsphenoidal adenomectomy by an experienced pituitary surgeon who performs this operation many times each year. For those patients who are not cured with pituitary surgery, other options such as medical treatment, radiation therapy and bilateral adrenalectomy are typically considered (1). For other tumor subtypes, such as acromegaly or prolactinomas, approved medications are available that treat the pituitary adenoma and control hormone excess. However, there is no medication currently approved for targeting the corticotroph adenomas which produce excess ACTH and result in Cushing's disease. Available medical therapies, such as ketoconazole or metyrapone, block adrenal production of cortisol via inhibition of enzymes in the steroid synthetic pathway. There is a clear need for effective medical treatments for corticotroph adenomas. This Journal Club focuses on two recent studies of agents which may hold promise in this regard.

The article entitled "*Treatment of Pituitary-dependent Cushing's Disease with the Multireceptor Ligand Somatostatin Analog Pasireotide (SOM230): A Multicenter, Phase II Trial*" by Boscaro *et al.* reports on a short-term Phase II trial with an investigational somatostatin analog (2). The rationale for using pasireotide relates to its somatostatin receptor binding specificity, which differs from the commercially available somatostatin analogs octreotide and lanreotide, the medications approved for acromegaly. Pasireotide has high binding affinity for four of the five somatostatin receptor subtypes (SSTRs 1-3 and 5), with particularly high affinity for SSTR5 in comparison to octreotide (3). Pituitary adenomas derived from corticotroph cells express SST5 receptors and *in vitro* studies have shown that pasireotide inhibits ACTH release from cultured corticotroph cells (4). These findings suggested a possible therapeutic role for pasireotide in Cushing's and led to a multicenter, international, Phase II trial.

The results of that trial are now reported by Boscaro *et al.*; the study enrolled 39 adults with *de novo* Cushing's, or with persistent or recurrent disease after transsphenoidal surgery (TSS). Entry criteria included a mean 24h urine free cortisol (UFC) from two collections of at least two-fold above the upper limit of normal and no history of radiation therapy. An independent review board confirmed the pituitary source of the disorder. Patients self-administered pasireotide subcutaneously at a dose of 600mcg bid for 15 days, with the primary endpoint being UFC normalization.

Figure 1 shows the change in UFC from baseline over 15 days of treatment. Five patients attained a normal mean UFC during the brief study, and UFC decreased in the majority (76%) of subjects.

Individual responses are shown in Figure 2. The medication was well-tolerated, with the most common side effects being gastrointestinal, typical for somatostatin analogs. Hyperglycemia was seen in 36% of patients. These data were considered a positive "proof of concept" study, and a Phase 3, international, multicenter trial is now underway.

One strength of this study was the strict entry criteria, which ensured that all treated subjects clearly had a pituitary source of Cushing's. A potential limitation of the study was the requirement that all patients have a mean UFC at least two-fold above the upper limit of normal. Many patients with Cushing's, particularly those who are not cured with TSS or have an early recurrence, have milder cortisol elevations. Because non-surgical treatments of acromegaly, including somatostatin analogs, have been shown to be more effective when the biochemical abnormalities are mild, it is possible that the high UFCs required for enrollment biased this study against showing maximum benefit. Nevertheless, the fact that 76% of patients exhibited a decrease in UFC with just 15 days of treatment suggests this investigational agent is worth exploring further. Questions to be addressed in future studies include how effective pasireotide will be in patients with Cushing's disease across the full spectrum of UFC elevation, whether the effect can be sustained over time, and whether it is safe, with particular attention to the effect on blood sugar.

In the same edition of *The Journal of Clinical Endocrinology and Metabolism*, an article by Pivonello *et al.* describes the use

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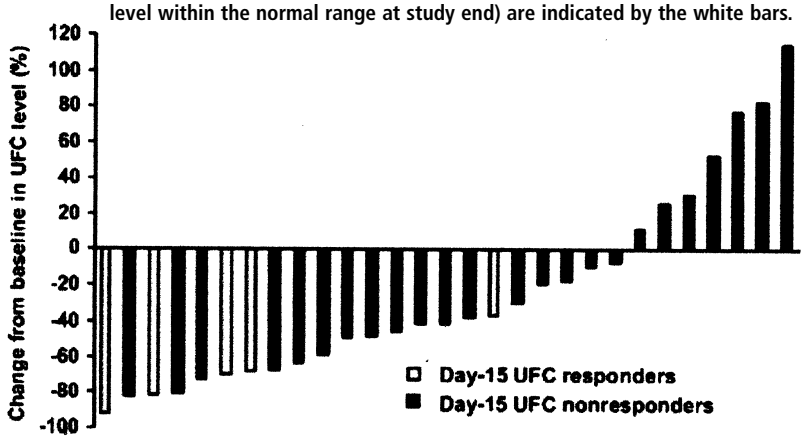
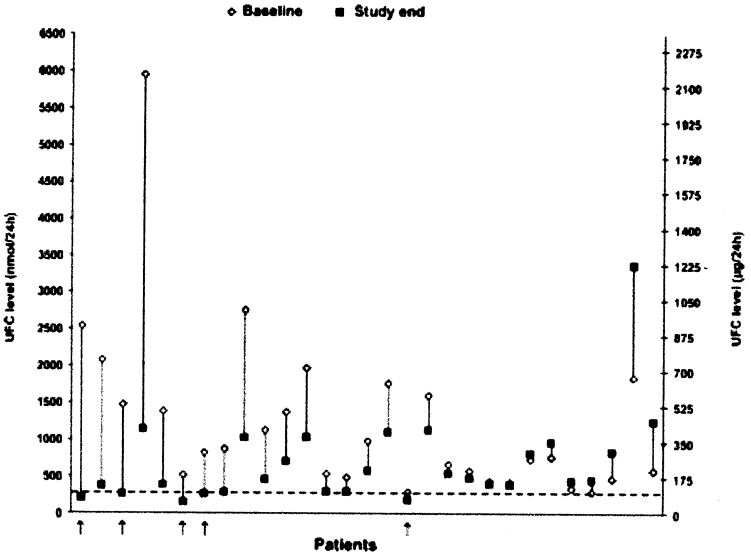
Figure 1 **Percent change from baseline in UFC level in patients who received pasireotide 600µg sc bid for 15 d (primary efficacy population, n=29). Responding patients (defined as having a UFC level within the normal range at study end) are indicated by the white bars.**



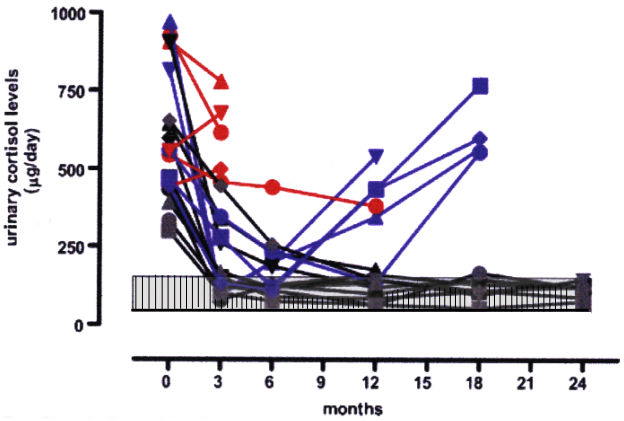
From Boscaro M et al. 2009. Treatment of Pituitary-dependent Cushing's Disease with the Multireceptor Ligand Somatostatin Analog Pasireotide (SOM230): A Multicenter, Phase II Trial. *J Clin Endocrinol Metab.* 94:115-22. *Copyright 2009, The Endocrine Society.*

Figure 2 **Mean UFC level at baseline and study end (d 15) in each patient (mean of two 24-h UFC level measurements). The normal range for UFC is 55–276 nmol/24 h (20–100µg/24 h); the *dashed line* indicates the upper limit of the normal range. Responding patients (defined as having a UFC level within normal range at study end) are indicated by *arrows*. Patients are presented in the same order as in Figure 1.**



From Boscaro M et al. 2009. Treatment of Pituitary-dependent Cushing's Disease with the Multireceptor Ligand Somatostatin Analog Pasireotide (SOM230): A Multicenter, Phase II Trial. *J Clin Endocrinol Metab*. 94:115-22. *Copyright 2009, The Endocrine Society.*

Figure 3 **Urinary cortisol levels during the entire period of treatment in all 20 patients treated with cabergoline. The patients long-term response to cabergoline treatment are shown with *black lines*, those with early response and late escape are shown with *purple lines*, and those nonresponders to the treatment are shown with *red lines*. The shaded area indicates the normal range of urinary cortisol levels (35–135µg/d). Urinary cortisol levels represent the mean of three different urine collections performed on three different nonconsecutive days of the same week.**



From Pivonello R et al. 2009. The Medical Treatment of Cushing's Disease: Effectiveness of Chronic Treatment with the Dopamine Agonist Cabergoline in Patients Unsuccessfully Treated by Surgery. J Clin Endocrinol Metab. 94: 223-230. *Copyright 2009, The Endocrine Society.*

of the dopamine agonist cabergoline for Cushing's disease (5). Dopamine receptors have been shown to be expressed on corticotroph adenomas (6), providing the scientific basis for using this class of drugs. Twenty patients who had not been cured with surgery and had a UFC at least two-fold above the upper limit of normal were enrolled and treated with cabergoline, starting at 1mg/wk (given biweekly), increasing by 1mg every month until mean UFC normalized or up to a maximum dose of 7mg/wk (given as 1mg daily).

Figure 3 shows the UFCs over the treatment period, with different colors representing three groups classified as long-term responders, early response with late escape, and nonresponders (5/20 with less than a 25% reduction in UFC). Eight of the patients (40%) showed sustained UFC control at two years, at a dose ranging between 1-7mg/wk (median 3.5mg/wk). One concerning finding was that among 15 patients with at least a 25% reduction in UFC over the first three months of treatment, five subsequently had a rise in UFC, termed "escape" by the authors. The presence of hyperprolactinemia did not predict long-term cortisol response. A total of seven patients withdrew for lack of response or intolerance. Two patients, who had responded, discontinued the medication between months 12-24 due to "severe asthenia associated with hypotension". A few patients experienced milder asthenia; other side effects included dizziness and nausea.

A strength of the study regarding safety monitoring, given recent concerns about valvulopathy in patients with Parkinson's disease treated with high doses of cabergoline, was that echocardiograms were performed at baseline and every six months (7,8). One patient progressed from mild tricuspid regurgitation (TR) at baseline to moderate TR after two years.

The long-term risk to cardiac valves will be important to consider if cabergoline is to be used in doses up to 7mg/wk for many years. Limitations in this report included the small number of subjects, the absence of data about whether anyone had received radiation treatment, and the lack of information as to whether the patients who dropped out may have been experiencing adrenal insufficiency. Further studies of this dopamine agonist as a potential treatment for Cushing's disease will need to address optimal dosing, explore whether the escape phenomenon is a common problem, and address the risks of hypoadrenalism and valvulopathy in a larger number of patients with a wide range of UFC elevations.

In summary, two articles from the January 2009 volume of *The Journal of Clinical Endocrinology and Metabolism* suggest the possibility of using medical treatments directed at the dopamine or somatostatin receptors on corticotroph adenomas. If these medications are proven both effective and safe in larger groups of patients, this would represent a major advance in the treatment of Cushing's disease, particularly in those patients who are not cured by surgery.

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RESEARCH STUDIES AVAILABLE

Patients may qualify for research studies in the Neuroendocrine Clinical Center. We are currently accepting the following categories of patients for screening to determine study eligibility. Depending on the study, subjects may receive free testing, medication and/or stipends.

SUBJECTS	STUDIES	CONTACT 617-726-3870
Newly diagnosed acromegaly	• Evaluating preoperative medical treatments	Karen Pulaski-Liebert, R.N. Dr. Beverly M.K. Biller
Cushing's Syndrome	• Evaluating a potential new medical therapy	Karen Pulaski-Liebert, R.N. Dr. Beverly M.K. Biller
Adolescent girls with anorexia nervosa	• Evaluating bone density and the effects of estrogen replacement • Newer therapeutic possibilities	Dr. Anne Klibanski Dr. Madhu Misra
Adolescent athletes	• Investigating impact of hormonal alterations on menstrual function and bone density	Dr. Madhu Misra Dr. Anne Klibanski
Adolescent boys and girls with depressive disorders	• Investigating impact of hormonal alterations on reproductive function and bone density	Dr. Madhu Misra Dr. Anne Klibanski
Women with anorexia nervosa	• New therapies	Dr. Karen K. Miller Dr. Anne Klibanski
Women and men, ages 18-45	• Investigating body weight and GH secretion • GH treatment in abdominal obesity	Dr. Karen K. Miller
Girls and women with current anorexia nervosa or a history of anorexia nervosa, ages 10 and up	• Investigating genetics of appetite-regulating and stress hormones	Dr. Elizabeth Lawson Dr. Karen K. Miller Dr. Anne Klibanski Dr. Madhu Misra
Healthy girls and women, ages 10 and up	• Investigating genetics of appetite-regulating and stress hormones	Dr. Elizabeth Lawson Dr. Karen K. Miller Dr. Anne Klibanski Dr. Madhu Misra
Women with a history of anorexia nervosa	• Investigating the link between cortisol regulation and bone density	Dr. Elizabeth Lawson Dr. Anne Klibanski
Women with irregular menstrual periods (hypothalamic amenorrhea), ages 18-45	• Investigating the link between cortisol regulation and bone density	Dr. Elizabeth Lawson Dr. Karen K. Miller Dr. Anne Klibanski
Obese men and women	• Use of GHRH, a growth hormone secretagogue, to increase endogenous GH levels, improve fat distribution and lipid profile • Assessment of relative GH levels and cardiac risk	Dr. Hideo Makimura
HIV positive men and women with fat redistribution	• Assessment of coronary artery atherosclerosis • Lifestyle modification strategies, including exercise and insulin sensitization	Dr. Steven Grinspoon Dr. Janet Lo Katie Fitch, ANP

SAVE THE DATE

SPECIAL LECTURE

Tenth Annual
Nicholas T. Zervas, M.D.
Lectureship

at the
Massachusetts General
Hospital

Historic Ether Dome

Tuesday, May 26, 2009
at 12 Noon

"Tailor-made GH Assessment
for GH Use and Abuse"

Christian J. Strasburger, M.D.
Professor of Medicine
Chief, Division of Endocrinology
Charite-Universitatsmedizin
Berlin, Germany

For further information
call Ivy at 617-726-9036

PHYSICIANS' PITUITARY INFORMATION SERVICE

Physicians with questions may contact:
Dr. Biller or Dr. Klibanski at
617-726-3965 or 1-888-429-6863
e-mail: pituitary.info@partners.org

SUPERVISING STAFF

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Helen A. Shih, M.D.

Psychiatry:
George Papakostas, M.D.

Pediatric Endocrinology
Madhusmita Misra, M.D., M.P.H.

SERVICES AVAILABLE

Facilities

The Neuroendocrine Center is located on the 1st floor (Suite 112) of Zero Emerson Place at the Massachusetts General Hospital. A test center is available for complete outpatient diagnostic testing, including ACTH (Cortrosyn) stimulation; insulin tolerance; CRH stimulation; oral glucose tolerance and growth hormone stimulation testing. Testing for Cushing's syndrome can also be arranged, including bilateral inferior petrosal sinus ACTH sampling for patients with ACTH-dependent Cushing's syndrome.

Neuroendocrine Clinical Conference

A weekly interdisciplinary conference is held to discuss all new patients referred to the Neuroendocrine Center and to review patient management issues. It is a multidisciplinary conference, attended by members of the Neuroendocrine, Neurology, Neurosurgery, Psychiatry and Radiation Oncology services. Physicians are welcome to attend and present cases.

Physicians' Pituitary Information Service

Physicians with questions about pituitary disorders may contact Dr. Biller or Dr. Klibanski at (617) 726-3965 within the Boston area or toll free at (888) 429-6863, or e-mail to pituitary.info@partners.org.

Scheduling

Outpatient clinical consultations can be arranged by calling the Neuroendocrine Center Office at (617) 726-7948.

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