MASSACHUSETTS GENERAL HOSPITAL

Neuroendocrine & Pituitary Tumor Clinical Center (NEPTCC) Bulletin

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Journal Club: Review of Levoketoconazole and Osilodrostat in the Treatment of Cushing's Syndrome

ALLISON KIMBALL, MD

Cushing's syndrome is a serious condition characterized by cortisol excess and associated with increased mortality, primarily related to cardiovascular disease (1, 2). The most common source of cortisol overproduction is a pituitary adenoma (Cushing's disease). Medical treatment is indicated for persistent or recurrent hypercortisolism following surgery, estimated to occur in one third of patients (3), or when surgery or radiation are contraindicated. Although several medications with different mechanisms of action are available, Cushing's syndrome is difficult to treat. Additional effective and well-tolerated medications are needed.

Results from phase 3 trials studying the efficacy and safety of two new pharmacologic treatments for Cushing's syndrome, levoketoconazole and osilodrostat, were recently published (4, 5), and a review of these studies follows.

SONICS (levoketoconazole)

Ketoconazole (a racemic mixture of the enantiomers 2S,4R-ketoconazole and 2R,4S-ketoconazole) inhibits several enzymes involved in adrenal steroidogenesis, leading to decreased cortisol production. It is not FDA-approved for the treatment of Cushing's syndrome in the US, although it is used off-label for this purpose. Important considerations are drug-drug interactions and side effects, and there is a black box warning for rare liver toxicity, which advises monitoring of liver function tests. While efficacy of ketoconazole has been established by retrospective and observational data, it has never been studied in a prospective clinical trial. The 2S,4R enantiomer of ketoconazole, levoketoconazole, is about twice as potent in vitro in inhibiting enzymes such as 17α-hydroxylase and 11β-hydroxylase, which makes it a promising pharmacologic treatment option (6).

SONICS was a multicenter, open-label, single-arm study of oral levoketoconazole in 94 adults with Cushing's syndrome who had mean 24-hour urinary free cortisol (UFC) >1.5 times the upper limit of normal (ULN) (4). Participants were treated with the starting dose of levoketoconazole 150 mg twice daily followed by titration over 2-21 weeks (in 150 mg increments until mean UFC normalization) before entering a 6-month maintenance phase. The primary outcome was the proportion of participants with mean UFC ≤ ULN at the end of the maintenance phase without requiring a dose increase during maintenance (complete response).

At baseline, mean age was 43.7 years and mean UFC was 4.9 times the ULN. Eighty-five percent of participants had pituitary Cushing's disease. Seventy-seven of 94 participants entered, and 61 completed, the maintenance phase. Mean UFC decreased quickly in the dose-titration phase and remained controlled from months 2-6 (Figure 1A). Twenty-nine of 94 participants (31%) experienced complete response (Figure 1B); the response rate was higher in participants with lower baseline mean UFC concentration. Improvements were seen in cardiovascular biomarkers, including HbA1c, fasting glucose, total and LDL cholesterol, and weight. Also improved were quality of life

and subjective signs and symptoms related to Cushing's syndrome. In general, levoketoconazole was well-tolerated and safe; the most common adverse events were headache and nausea.

The results suggest that levoketoconazole may be an effective treatment for Cushing's syndrome. Important limitations of this study include its open-label design and absence of a control group. Because there are no prospective studies assessing ketoconazole in Cushing's syndrome, comparison of levoketoconazole to ketoconazole is not possible.

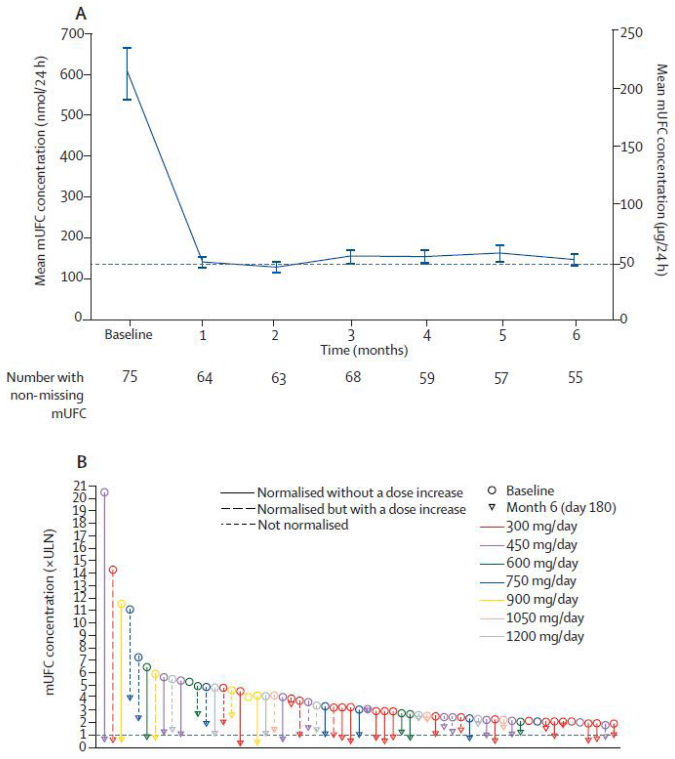

Figure 1. A) Mean UFC from baseline to the end of the maintenance phase. Dotted line represents the ULN for UFC (138 nmol/24 h [50 µg/24 h]). Error bars represent ± 1 SE. B) Change in individual mean UFC from baseline to the end of maintenance phase. Each vertical set of datapoints is for one subject. Abbreviations: mUFC=mean urinary free cortisol, ULN=upper limit of normal. Reproduced with permission from Fleseriu et al., Lancet Diabetes Endocrinol, 2019 (4).

LINC 3 (osilodrostat)

LINC 3 (5) was the first phase 3 study of a pharmacologic treatment in patients with Cushing's disease that included a double-blind, placebo-controlled withdrawal period. Participants received osilodrostat, which reversibly inhibits the enzyme 11-ß-hydroxylase that catalyzes the last step of cortisol synthesis.

In LINC 3, 137 adults aged 18-75 with recurrent or persistent Cushing's disease and mean 24-hour UFC >1.5 times the ULN were studied. Open-label oral osilodrostat was started at 2 mg twice daily and then adjusted every 2 weeks until week 12 (up to 30 mg twice daily) to normalize mean UFC (period 1). Osilodrostat was continued at the therapeutic dose from weeks 13-24 (period 2). At week 26, patients with mean UFC ≤ ULN at week 24 who did not require uptitration after week 12 were randomly assigned to continue osilodrostat or switch to placebo for 8 weeks (period 3). All participants received open-label osilodrostat from weeks 35-48 (period 4). The primary endpoint was complete response rate, defined as the proportion of participants who maintained mean UFC ≤ ULN at the end of the 8-week withdrawal period.

At baseline, median age was 40 years and mean UFC was 7.3 times the ULN. Seventy-two of 137 participants (53%) achieved complete response at week 24 and were therefore eligible for the randomized withdrawal phase; 36 participants continued osilodrostat and 35 were assigned to placebo. More participants who continued osilodrostat maintained a complete response at week 48 (86% versus 29% in placebo group; Figure 2). As in SONICS, cardiovascular-related metabolic parameters were assessed, and osilodrostat treatment was associated with improvements in fasting glucose, weight, total cholesterol, and systolic and diastolic blood pressure. Clinically meaningful improvements in depression and quality of life were also observed. The most common adverse events were nausea, headache, fatigue, and adrenal insufficiency. Although inhibition of 11-ßhydroxylase leads to the accumulation of precursors, most related side effects were mild. Both men and women experienced an increase in testosterone and 11% of women experienced androgenic side effects (acne, hirsutism), but this did not result in study discontinuation by any subject. Despite the expected increase in mineralocorticoids,

"Levoketoconazole and osilodrostat are promising pharmacologic therapies for Cushing's syndrome that result in rapid and sustained reductions in UFC."

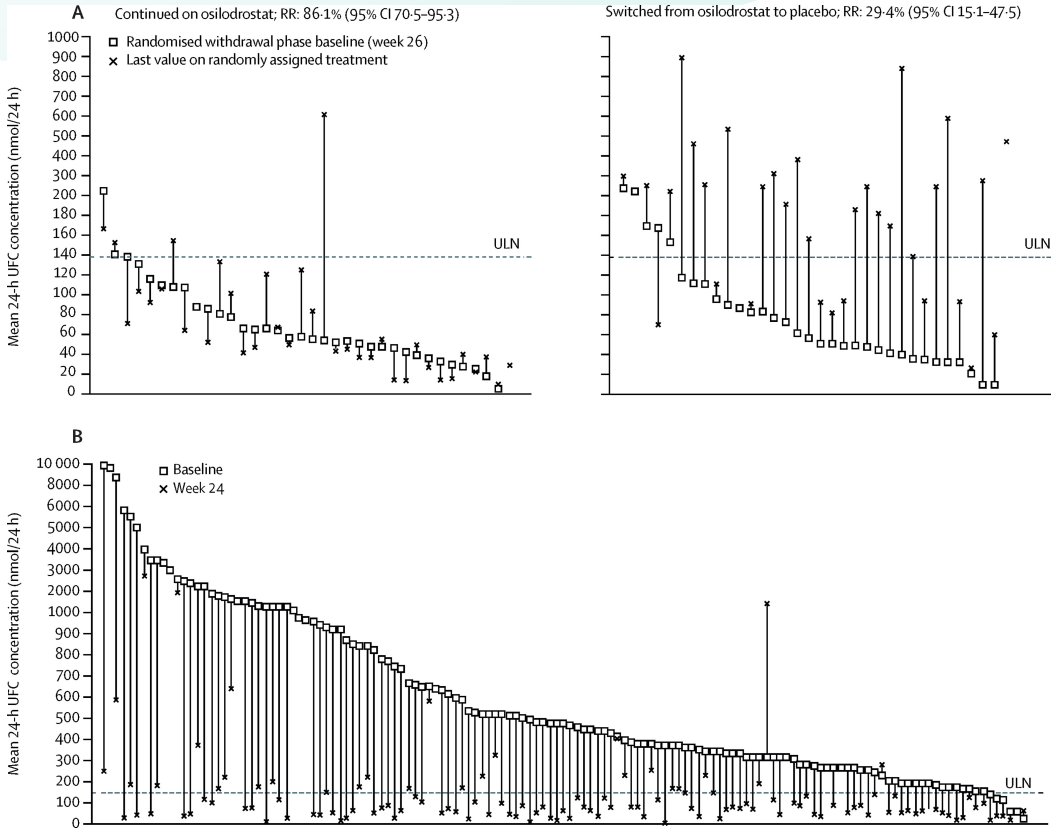

Figure 2. Changes in mean UFC during the withdrawal phase, by treatment group (A) and from baseline to week 24 (B). Each vertical set of datapoints is for one subject. For panel B, data are arranged from highest to lowest baseline mean UFC. Abbreviations: UFC=urinary free cortisol, RR=response rate, ULN=upper limit of normal. Reproduced with permission from Pivonello et al., Lancet Diabetes Endocrinol, 2020 (5).

hypertension and low serum potassium were not frequently reported among participants taking osilodrostat.

In conclusion, the results demonstrate that osilodrostat is effective in lowering mean UFC and improving clinical parameters associated with hypercortisolism. The double-blind, placebo-controlled withdrawal period was a strength of this study, although the short duration may explain why nearly a third of participants still had normal UFC after withdrawal of osilodrostat. Follow-up studies of osilodrostat to assess long-term efficacy and safety are warranted.

Summary

Levoketoconazole and osilodrostat are promising pharmacologic therapies for Cushing's syndrome that result in rapid and sustained reductions in UFC. Both have acceptable safety and tolerability profiles. Levels of adrenocorticotropic hormone (ACTH) rose in patients with Cushing's disease in both studies, as is expected with adrenal-blocking medications. Neither study was long enough to determine the risk of tumor enlargement. Levoketoconazole is not currently available in the United States. In March 2020, osilodrostat was FDA-approved for adults with Cushing's disease for whom pituitary surgery cannot be performed or has not been curative.

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Save the Date
SPECIAL LECTURE

22nd Annual Nicholas T. Zervas, M.D. Lectureship

Massachusetts General Hospital

Virtual Event

Tuesday, May 19, 2021 at 12pm

Maria Fleseriu, M.D, FACE
Professor of Medicine and Neurological Surgery and Director of the Northwest Pituitary Center at Oregon Health and Science University in Portland, Oregon

For further information call Philip at 617-726-3870

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On-line registration and program information will be available fall 2021; to be added to the mailing list before that, send a message to Course Administrator Melissa Machado at mmachado4@mgh.harvard.edu and 617-726-3270.

Potts Mentoring Award Announcement

Dr. Karen K.. Miller

On January 26th, 2021, Dr. Karen K. Miller, Chief of the MGH Neuroendocrine Unit, was honored with the MGH John T. Potts, Jr., MD Faculty Mentoring Award at the MGH Celebration of Mentoring event. The MGH Center for Faculty Development created the annual Award in 2011 to recognize a senior faculty member who has contributed to the success of junior faculty members and trainees. In accepting the award, Dr. Miller thanked those who had nominated her and her mentor, Dr. Anne Klibanski, former Chief of the MGH Neuroendocrine Unit and current President and CEO of Mass General Brigham, "who modeled mentoring so beautifully." She added, "The real gift is to have had the honor to mentor and co-mentor so many talented and hardworking individuals...to be a part, however small, of their great work and to be entrusted with their careers."

Role of Growth Hormone in Nonalcoholic Fatty Liver Disease (NAFLD)

LINDSAY T. FOURMAN, MD

Nonalcoholic fatty liver disease (NAFLD) is a common disorder.

Characterized by hepatocellular triglyceride accumulation in the absence of significant alcohol consumption, NAFLD is the most common liver disease in the U.S., with an estimated prevalence of 30% (1). NAFLD is associated with obesity and metabolic syndrome, and is an independent risk factor for coronary artery disease. NAFLD also may progress to cirrhosis or hepatocellular carcinoma, and is expected to surpass hepatitis C as the principal indication for liver transplantation within the next decade (2). Despite its growing threat to public health, the pathogenesis and effective management of NAFLD remain poorly understood. There also is no approved pharmacologic intervention for NAFLD with treatment recommendations focused on lifestyle modification, which may be difficult to achieve (3).

Growth hormone deficiency plays a role in NAFLD pathogenesis.

Pituitary growth hormone (GH) deficiency is characterized by enhanced visceral adiposity, reduced lean body mass, and dyslipidemia. Recent evidence also suggests that GH deficiency is a risk factor for NAFLD. In one case-control study, the prevalence of NAFLD was a striking 77% among consecutive patients with GH deficiency, which constituted a 6.4-fold increase compared to controls matched for age, sex, and BMI. Notably, in this study, treatment of a small subset of these individuals with GH led to a reduction in steatosis and fibrosis on liver biopsy (4). Relatedly, mice with liver-specific knockout of the GH receptor demonstrated increased liver fat and inflammation. These mice further demonstrated significant perturbations in lipid metabolism as characterized by upregulation of genes involved in hepatic lipid uptake and de novo lipogenesis. In this prior study, restoration of hepatic insulin-like growth factor 1 (IGF-1) expression only partially reversed the NAFLD phenotype, suggesting contributions of both components of the GH/IGF-1 axis to the pathogenesis of this disease (5).

Abdominal fat accumulation contributes to relative GH deficiency.

Given the role of GH in abdominal and hepatic fat accumulation among patients with hypopituitarism, our group and others have sought to understand whether individuals with abdominal obesity may exhibit perturbed GH secretion in the absence of known pituitary disease. Our work in this area has primarily focused on the HIV population given the predisposition toward abdominal fat accumulation among these patients (6). In a detailed physiology study, we found that individuals with HIV-associated abdominal adiposity demonstrated intact GH pulsatility but diminished pulse amplitude as measured by frequent overnight sampling. Mean GH levels among these subjects inversely correlated with visceral fat content (7). Mechanistically, individuals with abdominal obesity were found to have elevated circulating free fatty acids, increased somatostatin tone, and reduced ghrelin levels, which collectively acted to inhibit central GH secretion (8). Blunted GH secretion in the context of obesity serves as an important caveat to dynamic testing for GH deficiency, and as a consequence a higher threshold to diagnose GH deficiency in patients with pituitary disease and higher BMI has been advised (9). Nonetheless, relative GH deficiency among patients with obesity, even in the absence of true pituitary disease, may have important clinical consequences. Accordingly, growing evidence suggests that GH/IGF-1 is inversely associated with hepatic fat content, systemic inflammation, and vascular disease among populations with abdominal fat accumulation (10-12), akin to findings in patients with hypopituitarism.

Restoring GH pulsatility reverses metabolic dysfunction.

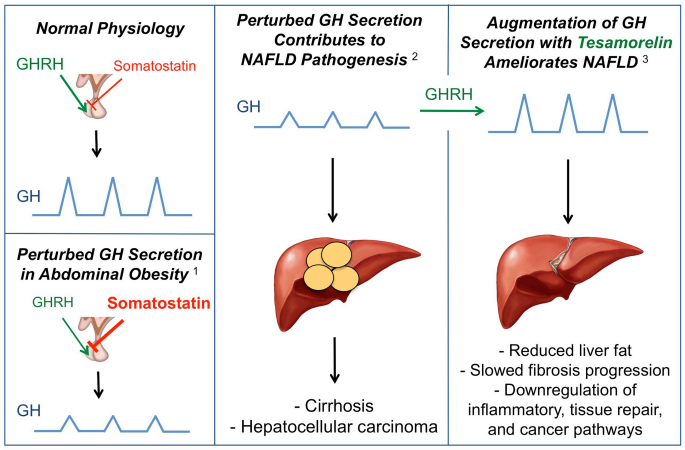
As a strategy to restore normal GH pulse dynamics among individuals with abdominal fat accumulation with intact pituitary function, our group employed the growth hormone-releasing hormone (GHRH) analogue, tesamorelin. GHRH analogue therapy offers several putative advantages to exogenous GH by allowing GH secretion to remain under the regulation of the pituitary gland. As such, GH pulsatility remains intact, consistent with normal physiology, which may have critical implications for GH action (13). GH secretion also remains under the influence of negative feedback by IGF-1, which minimizes the risk of iatrogenic GH/IGF-1 excess. In two large Phase III studies among individuals with

HIV and abdominal fat accumulation, tesamorelin was found to selectively reduce visceral fat by an estimated 15% over 26 weeks without substantially altering subcutaneous fat. Notably, tesamorelin also decreased serum triglycerides and preserved glucose homeostasis (14). As such, tesamorelin was FDA approved in 2010 for the treatment of abdominal fat accumulation in HIV. A randomized controlled trial in the non-HIV obese population demonstrated similar effects (15).

GHRH analogue tesamorelin serves as a novel hormonal strategy to ameliorate NAFLD.

Based on the role of GH in NAFLD pathogenesis, we recently hypothesized that augmentation of endogenous GH pulsatility with tesamorelin may ameliorate NAFLD. Accordingly, we randomized 61 individuals with HIV-associated NAFLD based on hepatic fat fraction ≥ 5% in the absence of other causes of hepatic steatosis to either tesamorelin or identical placebo for 1 year. Body composition or growth hormone parameters were not criteria for enrollment. We found that tesamorelin led to a -37% (95% CI -67 to -7) relative change in hepatic fat fraction. Relatedly, 35% of individuals assigned to tesamorelin had resolution of NAFLD over the course of the study compared to 4% of individuals assigned to placebo (p = 0.0069). Importantly, we also found that tesamorelin prevented progression of fibrosis; over the study period, 10.5% of individuals in the tesamorelin arm showed an increase in fibrosis stage versus 37.5% of individuals receiving placebo (p = 0.044). Given that hepatic fibrosis is a major predictor of liver-specific and all-cause mortality, these findings have exciting implications for prognosis in patients with HIV-associated NAFLD (16). As in the Phase 3 studies of abdominal obesity, tesamorelin was well tolerated with neutral effects of blood glucose. A randomized placebo-controlled trial is now underway to study the effects of tesamorelin on NAFLD among individuals without known HIV infection (NCT03375788).

Role of Growth Hormone in NAFLD Pathogenesis and Treatment



[1] Rietschel, *JCEM* 2001; Koutkia, *Am J Physiol Endocrinol Metab* 2004
[2] Stanley, *JAMA* 2014
[3] Stanley and Fourman, *Lancet HIV* 2019; Fourman, *JCI Insight* 2020

Augmenting GH pulsatility has effects on key hepatic pathways in NAFLD.

To enhance our knowledge of the effects of augmented pulsatile GH secretion on hepatic physiology in NAFLD, we leveraged paired liver biopsy specimens from our recent clinical trial to investigate differential changes in hepatic gene expression by tesamorelin versus placebo over one year. Using gene set enrichment analysis, we found that tesamorelin increased hepatic expression of gene sets involved in oxidative phosphorylation, and decreased hepatic expression of gene sets contributing to inflammation, tissue repair, and cell division. Tesamorelin also reciprocally up- and downregulated gene sets associated with favorable and poor hepatocellular carcinoma prognosis, respectively. Importantly, among tesamorelin-treated participants, these changes in hepatic expression correlated with improved fibrosis as measured by a previously validated gene score (17). Further building on this work, we recently performed a focused proteomic analysis of top leading edge genes within differentially modulated gene sets. Using this approach, we showed that GH axis augmentation had novel effects to reduce circulating levels of key angiogenic, pro-inflammatory, and fibrogenic mediators in association with an improvement in NAFLD activity among our participants with HIV-associated NAFLD (18).

Conclusions

While NAFLD remains an enigmatic disease, growing evidence suggests a role for GH in its pathogenesis and treatment. In patients with GH deficiency and hypopituitarism, data clearly indicate a heightened susceptibility to NAFLD. As such, it may be appropriate to screen such patients for this comorbidity and to strongly consider GH replacement in those found to have the condition. Furthermore, even in patients without pituitary disease, functional GH deficiency in the context of abdominal adiposity may be an important contributor to NAFLD pathogenesis. Importantly, our recent data in HIV suggest that augmentation of endogenous GH secretion with the GHRH analogue tesamorelin ameliorates the clinical

course of NAFLD, reducing not only liver fat but also fibrosis progression, and has broad effects on hepatic gene expression signatures. Thus, observations from patients with hypopituitarism have translated to advances in the obesity arena, revealing that functional defects in GH secretion among individuals with abdominal obesity may be pharmacologically targeted for treatment of metabolic comorbidities.

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Research Studies Available

The Neuroendocrine and Pituitary Tumor Clinical Center is involved in many different research studies. Types of studies and enrollment status changes frequently, so please call our office (617-726-3870) or search from a list of clinical studies (https://www.clinicaltrials.gov).

Welcoming Our New Staff Members

Dr. Allison Kimball

Dr. Allison Kimball earned her medical degree at Boston University School of Medicine. She completed her Internal Medicine residency training at Beth Israel Deaconess Medical Center and her Endocrinology fellowship training at Massachusetts General Hospital. Dr. Kimball is the Assistant Clinical Director of the MGH Neuroendocrine and Pituitary Tumor Clinical Center, where she sees patients with neuroendocrine and pituitary disorders. She also sees patients with diabetes at the MGH Diabetes Center and provides endocrine consultations on patients hospitalized at MGH. She has a focus in medical education, teaching medical students at Harvard Medical School and residents and other trainees at MGH. Dr. Kimball additionally performs clinical research in the MGH Neuroendocrine Unit.

Dr. Armen Yerevanian

Dr. Armen Yerevanian earned his medical degree at Case Western Reserve University School of Medicine. He completed internal medicine residency at Harbor-UCLA Medical Center where he also served as chief resident. His fellowship in Endocrinology, Diabetes and Metabolism was conducted at Massachusetts General Hospital. He currently sees patients in the MGH Neuroendocrine and Pituitary Tumor Clinical Center as well as the MGH Diabetes Center. His research interests involve the hormonal regulation of adipose tissue and metabolism.

SERVICES AVAILABLE

FACILITIES

The Neuroendocrine and Pituitary Tumor Clinical Center is located on the 1st floor (Suite 140) of the Cox Building at the Massachusetts General Hospital. A test center is available for complete outpatient diagnostic testing, including ACTH (Cortrosyn) 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 AND PITUITARY TUMOR CLINICAL CONFERENCE

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

PHYSICIANS' PITUITARY INFORMATION SERVICE (PPIS)

Physicians with questions about pituitary disorders may contact the PPIS 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 and Pituitary Tumor Clinical Center Office at (617) 726-7948.

The MGH Neuroendocrine and Pituitary Tumor Clinical Center Bulletin was supported in part by unrestricted educational grants from Ascendis, Crinetics and Ionis Pharmaceuticals. Other financial relationships may exist between these companies and The Massachusetts General Hospital.

Dr. Beverly MK Biller, Editor of the MGH Neuroendocrine and Pituitary Tumor Clinical Center Bulletin, has been the primary investigator on research grants to the Neuroendocrine Unit from Crinetics, Ionis Pharmaceuticals, Millendo, and Novartis and occasionally consults for Crinetics, Ipsen, Merck-Serono, NovoNordisk, and Recordati.

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