compared with placebo (p<0.05), with no difference in 2-hour glucose levels between groups at 6 months. Baseline fasting glucose predicted a 6-month change in 120 minute glucose levels within the growth GH (r=0.48; p=0.01). Five subjects had a 120-minute glucose level greater than 200 mg/dL, one of whom was on placebo. No subjects had fasting glucose levels ≥126 mg/dL. Additional side effects were limited.

Based on these findings, the authors concluded that GH replacement in viscerally obese premenopausal women has beneficial effects on markers of CV risk and body composition but is associated with a decrease in glucose tolerance in a minority of women.

*Note: Another term for SDS is z-score. The IGF-1 standard deviations score, or z-score, is a measure of how normal/abnormal the IGF levels are compared with a normal-for-age level; eg, an IGF-1 SDS of 0 is normal for age, but a SDS of -2 means that the IGF-1 level is 2 SD below the mean.

Pasireotide May Provide Option for Medical Therapy Targeting the Underlying Cause of Cushing Disease

Written by Lori Alexander

A Phase 3 trial showed that pasireotide, a multireceptor-targeted somatostatin analog, led to rapid and sustained decreases in cortisol levels and provided clinical benefit in patients with Cushing disease. Surgery is the first-line treatment for this disease, and most current medical options block adrenal cortisol production but do not treat the underlying disease. Pasireotide may provide the first reliable pituitary-directed medical therapy that targets the underlying cause of Cushing disease.

Beverly M.K. Biller, MD, Neuroendocrine Clinical Center, Massachusetts General Hospital, Boston, Massachusetts, USA, explained that pasireotide has high affinity for sst_5, the most prevalent somatostatin receptor on adrenocorticotropic hormone-secreting pituitary adenomas. The drug was found to inhibit production of adrenocorticotropic hormone in corticotroph adenomas *in vitro* and was promising in a 15-day Phase 2 study.

The multicenter Phase 3 trial included 162 patients with persistent/recurrent Cushing disease (n=135) or patients with *de novo* disease who were poor surgical candidates, refused surgery, or had surgically unapproachable tumors (n=27). The patients were randomly assigned in a double-blind manner to receive pasireotide at a dose of 600 µg (n=82) or 900 µg (n=80) subcutaneously twice a day. At 3 months, a urinary free cortisol (UFC) level was determined. If the level was ≤2 times the upper limit of normal (ULN; defined as 145 nmol/24 hr) and was less than the baseline level, the randomly assigned dose was continued (double-blinded) until Month 6. The study was unblinded for all other patients, and the dose was increased by 300 µg twice daily, with treatment continuing until Month 6. These latter patients were considered to be nonresponders for the primary efficacy analysis. Months 6 to 12 were open-label, with the dose titrated as needed. The primary endpoint was a UFC level less than the ULN at 6 months without the need for an increase from the randomized dose.

At 6 months, the primary endpoint was met in 14.6% of the patients in the 600-µg group and in 26.3% in the 900-µg group; the results at 12 months were similar (13.4% and 25.0%, respectively), confirming the durability of the effect. The predetermined criterion for the primary endpoint (a lower bound of the 95% CI>15%) was met for the 900-µg group (Table 1). The median decrease in UFC from baseline to Month 6 was approximately 48% for both groups. Higher rates of UFC normalization were associated with lower baseline levels of UFC. Patients who had an inadequate biochemical response could be identified on the basis of UFC levels within 1 to 2 months with 90% accuracy.

Table 1. Results of Primary Endpoint at Six Months.*

Twice-daily dose	No. (%) of Responses	95% CI
600 µg (n=82)	12 (14.6)	7.0 to 22.3
900 µg (n=80)	21 (26.3)	16.6 to 35.9
Overall (n=162)	33 (20.4)	14.2 to 26.6

*The predetermined criterion for the primary endpoint was a lower bound of the 95% CI>15%.

Pasireotide was associated with significant improvement in signs and symptoms of hypercortisolism, regardless of whether a normal UFC level was achieved. At Month 12, there were substantial decreases in blood pressure, low-density lipoprotein-cholesterol level, and body weight, as well as an increase in the health-related quality of life. Dr. Biller noted that the safety profile of the drug was generally similar to that of other somatostatin analogs, with the important exception of an increased frequency of hyperglycemia. At least 1 hyperglycemia-related adverse event occurred in 73% of patients overall. There were no cases of diabetic ketoacidosis or hyperosmolar coma, and the fasting glucose levels returned to baseline once pasireotide was discontinued. Gastrointestinal events occurred frequently, with 58% of patients overall reporting diarrhea and 52% reporting vomiting. As expected with an effective treatment for Cushing disease, hypocortisolism occurred in some patients (8%); this complication responded to dose reduction and/or temporary corticosteroid substitution.