A Prospective Trial With Ketoconazole Induction Therapy and Octreotide Maintenance Treatment of Cushing's Disease

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Context: The lack of efficacy of octreotide in the medical treatment of Cushing's disease (CD) may result from suppressive effects of hypercortisolism on somatostatin receptor subtype 2 (SST2) expression by corticotroph adenomas. We previously demonstrated that SST2 mRNA expression levels in corticotroph tumor cells from patients preoperatively treated with cortisol-lowering therapy are significantly higher compared to those from patients with uncontrolled CD at time of surgery. It may be hypothesized that control of cortisol production induced by steroidogenesis inhibitors may reverse SST2 expression and increase efficacy of tumor-directed therapy with octreotide. **Objective:** To evaluate the efficacy of a sequential strategy of initiation treatment with ketoconazole (KTC) to reduce cortisol levels, followed by octreotide as maintenance therapy in patients with CD. **Patients and Design**: 14 adult patients with CD were prospectively enrolled. All patients started on KTC (600-800 mg/day), and once cortisol levels were normalized, octreotide 20 mg/4 weeks was initiated which could eventually be increased to 30 mg/4 weeks. After two months of combined therapy, patients were maintained on octreotide monotherapy until the end of the study period (9 months). Treatment success was assessed by the mean of 2 collections of urinary free cortisol (UFC) levels. **Results:** The mean age of our study population (14 patients) was 48.6 years, 64% (n=8) were female, 85% (n=12) were newly diagnosed and naïve in treatment. Ketoconazole was able to normalize UFC level in 11 (79%) patients. Subsequently, octreotide effectively sustained normal UFC levels in 3 patients (27%) (responders). Four (36%) other patients showed a partial response to octreotide. In 3 patients, normal UFC levels were sustained for one- or two-months following discontinuation of KTC and in the other partial responder, the UFC levels at follow-up decreased by at least 50% of the baseline levels. The remaining 4 (36%) patients developed hypercortisolism as soon as ketoconazole was stopped (non-responders). Responders to octreotide had lower UFC levels at baseline when compared to partial and non-responders (1.40 ± 0.06 vs. 2.05 ± 0.20 ULN, p=0.08). Two of three responders showed improvement in weight, waist circumference, and systolic and diastolic blood pressure during the treatment period. In terms of side effects, one patient discontinued KTC because of gastrointestinal intolerance and 5 patients had a transient increase in liver enzymes. **Conclusions:** This proof-of-concept study shows that the sequential treatment with ketoconazole to lower cortisol levels followed by octreotide to maintain normal cortisol production seems effective in a subset of patients with mild CD. Ongoing studies aim to evaluate whether this is the result from increased SST2 expression in corticotroph adenomas.

Neuroendocrinology and Pituitary

CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY

Addition of Cabergoline to Oral Octreotide Capsules May Improve Biochemical Control in Patients With Acromegaly Who Are Inadequately Controlled With Monotherapy

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Background: Oral octreotide capsules (OOC; MYCAPSSA®) are approved in the US for individuals with acromegaly who responded to and tolerated treatment with injectable somatostatin receptor ligands (iSRLs). Add-on cabergoline therapy has shown effectiveness in patients previously inadequately controlled with iSRLS.[1] The phase 3 MPOWERED trial assessed maintenance of response with OOC compared to iSRLs. Patients receiving OOC and ineligible for randomized controlled treatment (RCT) phase were eligible for a sub-study evaluating combination therapy with cabergoline, a dopamine agonist.
Methods: Patients who fail to respond to 80 mg/d OOC for ≥2 weeks during the 26-week Run-in phase, or ineligible to enter the RCT on 80 mg/d OOC, due to inadequate biochemical control (insulin-like growth factor I [IGF-I] ≥1.3 × upper limit of normal [ULN] to <2 × ULN or IGF-I <1.3 × ULN and mean integrated growth hormone [GH] ≥2.5 ng/mL) were eligible for sub-study combination OOC 80 mg/d and cabergoline ≤3.5 mg/wk (fixed algorithm) for 36 weeks. End points included categorical changes in IGF-I and mean GH levels at sub-study end and adverse event (AE) incidence and severity. Echocardiogram was performed at sub-study start and every 12 weeks after.
Results: Of 146 patients enrolled in MPOWERED, 14 entered the combination sub-study, 9 having IGF-I ≥1.3 × ULN at sub-study start. Final cabergoline doses were 1 (n=5), 2 (n=3), 3 (n=1), and 3.5 mg (n=5) with 25.4-week (SD, 14.1) mean treatment duration. Week 36 IGF-I improved

in most patients (n=12; 85.7%). Of 9 patients with IGF-I ≥1.3 × ULN at sub-study start, 5 (55.6%; 95% CI, 21.2%-86.3%) exhibited IGF-I decreased to predefined responder range (<1.3 × ULN) by week 36. AE incidence and nature with combined treatment were similar to known octreotide safety profile and acromegaly disease burden. There were no serious AEs or AEs leading to discontinuation of either sub-study drug.

Conclusion: We have shown for the first time the benefit of an all-oral combination treatment for acromegaly and avoidance of injection-related burdens. Addition of cabergoline to OOC yielded biochemical control improvement (IGF-I reduction) in patients inadequately controlled with OOC monotherapy. As both combination and OOC monotherapy safety profiles were similar, adjunctive cabergoline may be helpful in patients with acromegaly who do not achieve adequate biochemical control on OOC alone.

[1]Giustina A, et al. *Nat Rev Endocrinol.* 2014;10(4):243-248.

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CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY

Clinical Correlation to E-cadherin and Granulation Patterns in Corticotroph Tumors

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Corticotroph adenomas, either secretory or silent, are associated with significant disease persistence and/or recurrence. Surgical resection is the first line treatment; however, recurrence rates range from 30 to 60%. Although several clinical parameters (i.e. postoperative cortisol level, tumor invasion) have been reported to predict tumor recurrence, none have high diagnostic accuracy. Granulation pattern classifies corticotroph tumors as densely granulated (DG) or sparsely granulated (SG) types, with the latter usually larger and more aggressively behaving. E-cadherin, a calcium-dependent adhesion molecule strongly expressed in normal pituitary cells, plays a role in epithelial cell behavior, tissue development, and suppresses epithelial-mesenchymal transition. Since loss of E-cadherin expression in sparsely granulated somatotroph pituitary tumors correlates with a more aggressive disease course, we sought to examine correlation between E-cadherin expression and behavior in densely versus sparsely granulated corticotroph tumors. A retrospective chart review of adult patients with corticotroph adenomas, seen at our institution between January 2012 - 2020 yielded 62 patients: 18 (29%) male and 44 female (71%), with median age at diagnosis of 49 years (range 25-82). Inclusion criteria required sufficient tissue for E- cadherin immunostaining (IHC). Microadenomas were identified in 19/62 (31%) patients, and 38/62 (52%) patients had clinical and biochemical findings consistent with excess cortisol secretion. Pre-operative imaging showed that 22/62 (35%) tumors were invasive into surrounding structures. After further classification as to densely granulated (DG) or sparsely granulated (SG) types by ACTH granulation pattern on IHC, 19/56 (34%) adenomas were SG, 37/56 (66%) were DG and 6 were not classified. E-cadherin staining was absent in 7/62 tumors (11%) and diminished in 5/62 (8%) tumors and staining did not correlate with dense versus sparse corticotroph types. Chi-squared analysis found a significant association between tumor size (greater than or less than 1cm) and secretion, with hormonally active more likely tumors to be microadenomas (p=0.004). Microadenomas were exclusively DG tumors (p<0.001). Further analysis did not find correlation between presence or absence of E-cadherin expression and tumor invasion into adjacent structures, or recurrence. In summary, the data suggests that, unlike somatotroph corticotroph adenomas for recurrence or invasion, nor does it correlate strongly with granulation status.

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CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY

Design of the ForesiGHt Trial: A Multicenter, Randomized, Placebo- and Active-Controlled Trial to Compare Once-Weekly TransCon hGH (lonapegsomatropin) to Placebo and Daily Somatropin in Adults With Growth Hormone Deficiency (GHD)

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BackgroundAdult GHD results from insufficient growth hormone (GH) secretion from the anterior pituitary gland and may represent either a continuation of childhood-onset GHD or GHD acquired during adulthood. Clinically, adult GHD is associated with central adiposity, decreased lean muscle mass, increased fat mass, decreased bone mineral density, and reduced quality of life. Current standard of care consists of GH replacement via daily injections.

Lonapegsomatropin is a long-acting prodrug of somatropin (hGH), designed to deliver unmodified hGH with a weekly exposure profile. Lonapegsomatropin consists of somatropin that is transiently bound to a carrier via a proprietary TransCon Linker. The carrier extends the duration of somatropin in the circulation through a shielding effect that minimizes renal excretion and receptor-mediated clearance of the prodrug. At physiologic conditions, lonapegsomatropin releases fully active, unmodified somatropin via autocleavage of the linker in a controlled manner.

The safety and efficacy of lonapegsomatropin have previously been evaluated in two phase 3 trials and one long-term extension trial in pediatric GHD. Changes in body