which have been engineered to improve protein stability and solubility in solutions containing preservatives, are currently in human clinical trials. In addition, in vivo FGF21 gene therapy using viral vector is being explored as an alternative therapeutic approach. In this study, we present a simpler method of in vivo FGF21 gene therapy, in which liver-specific delivery of an unpackaged plasmid construct expressing an HA-tagged FGF21 protein increases de novo hepatic FGF21 production and secretion in mice. Our data show that FGF21 protein expression can be successfully restored into the livers of FGF21 conditional knockout mice for at least two weeks after a single tail vein injection with the expression plasmid, and that the HA-tagged protein is secreted and readily detectable in serum. In wild-type C57BL6/J mice, in vivo plasmid delivery significantly increased hepatic FGF21 protein 2.3-fold after two weeks, and was associated with reduced body mass and a 14% reduction in fasting serum glucose. In addition, elevated hepatic FGF21 levels correlated with a 27% decrease in the ratio of fat to body mass, visibly smaller subcutaneous and visceral white fat adipocytes, and a 3.3-fold increase in uncoupling protein 1-dependent mitochondrial respiration in the white fat. Together, these data suggest that in vivo plasmid delivery may potentially be an effective strategy for promoting hepatic FGF21 expression in models of obesity. We are currently testing this hypothesis with experiments in high-fat diet-challenged mice.

Neuroendocrinology and Pituitary

PITUITARY TUMORS: TRIALS AND STUDIES

Post-Operative Day One Morning Cortisol Value as a Biomarker to Predict the Recurrence of Cushing Disease

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OR23-03

Tumor removal by transsphenoidal surgery (TSS) is the first line treatment for Cushing disease (CD). However, recurrence is relatively common. A one week post-operative (post-op) nadir cortisol has been used as a biomarker to predict recurrence[1]. We identified 299 CD patients from our longitudinal multidisciplinary clinic or our institutional RPDR search tool who met biochemical diagnostic criteria[1] and had undergone TSS between May 2008 and May 2018, to evaluate post-op cortisol levels as biomarkers to predict long-term remission and to characterize clinical features of Cushing syndrome. Predictors of recurrence were identified with logistic regression, using recurrence as the dependent variable, and a Kaplan-Meier survival curve analysis was performed to compare long-term remission after TSS among the 202 patients who reached initial remission and had at least 1 year of follow-up. The post-op day 1 morning (AM) cortisol had significant association with CD recurrence (OR=1.025, 95%CI:1.002-1.048, p=0.032). The time to recurrence was significantly longer in patients with post-op day 1 AM cortisol <5 μg/dL. In contrast, one week post-op nadir cortisol (OR=1.081, 95%CI: 0.989-1.181, p=0.086), urinary free cortisol (OR=1.032,95%CI: 0.994-1.07, p=0.098), or late night salivary cortisol (OR=1.383, 95%CI:0.841-2.274, p=0.201) had no significant correlation with recurrence. There were no significant differences in time to recurrence for post-op day 2 AM cortisol <5 μg/dL. Among patients who developed post-op adrenal insufficiency, recurrence was significantly lower if glucocorticoid replacement continued for more than one year. In addition, tumor proliferative index (MIB-1) had a significant correlation with recurrence (OR=1.287, 95%CI:1.106-1.498, p=0.001). The most common symptoms and signs of initial presentation of CD were weight gain (91.6%), central obesity (79.6%), menstrual disorders (77.9%), round face (65.9%), hypertension (63.2%), mood disorders (60.2%), dorsocervical fat deposition (59.9%), supraclavicular fat deposition (59.9%), osteoporosis (58.9%), fatigue (58.2%), bruising (55.9%) and facial hirsutism (54.2%). Most of the best discriminating CD features did not have high sensitivity, such as purple striae (31.4%), facial plethora (33.4%) and proximal muscle weakness (30.8%). Our data show that post-op day one morning cortisol level above 5 μg/dL had significant association with recurrence. In contrast, the one week post-op nadir cortisol level had no significant value to predict recurrence. Our data also suggest that nonspecific symptoms and signs of CD are more common than stereotypical signs. **Reference:** Nieman LK, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015; 100:2807-2831

Thyroid

BENIGN THYROID DISEASE AND HEALTH DISPARITIES IN THYROID I

Pharmacokinetics (PK) and Exposure-Response Relationship of Teprotumumab, an Insulin-Like Growth Factor-1 Receptor (IGF-1R) Blocking Antibody, in Active Thyroid Eye Disease (TED)

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SAT-432

Introduction: Teprotumumab treatment resulted in statistically and clinically meaningful improvements across multiple facets of active TED and was generally well-tolerated in Phase 2 and 3 trials.[1,2] An initial intravenous infusion of 10 mg/kg followed by 20 mg/kg every 3 weeks was selected based on in vitro activity and clinical PK profile, to maintain pharmacologically active exposures and >90% saturation of IGF-1R over dosing intervals and to achieve efficacy at a well-tolerated dose for this vision-threatening disease.

Methods: Population PK analysis were performed on data from a Phase 1 oncology study (n=60)[3] and Phase 2 and 3 trials in active TED (N=83)[2,3] and covariate effect

on PK was assessed. Exposure-response relationship was evaluated in TED studies for key efficacy endpoints (proptosis response rate, % patients with a clinical activity score value of 0 or 1, and diplopia responder rate) and selected safety variables (hyperglycemia and muscle spasms).

Results: Teprotumumab PK was linear in TED patients and consistent with other immunoglobulin G1 monoclonal antibodies (IgG1 mAbs), with low systemic clearance (0.334 L/day), low volume of distribution (3.9 L for central compartment and 4.2 L for peripheral compartment), and long elimination half-life (19.9 days). [4,5] Model-predicted mean (± standard deviation) steady-state area under the concentration curve (AUC_{ss}), peak ($C_{max,ss}$), and trough ($C_{min,ss}$) concentrations in TED patients were 131 (± 30.9) mg·hr/mL, 643 (± 130) µg/mL and 157 (± 50.6) µg/mL, respectively, suggesting low inter-subject variability.

Population PK analysis indicated no significant impact of baseline age, gender, race, weight, smoking status, renal impairment (mild/moderate), and hepatic function (total bilirubin, aspartate and alanine aminotransferases) on teprotumumab PK. Female patients had 15% higher $C_{max,ss}$ but similar AUC compared to male patients, which is not considered clinically relevant.

Exposure-response analysis from the TED dose regimen indicated no meaningful correlations between exposures (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) and key efficacy endpoints or selected safety variables, supporting the demonstrated, favorable benefit-risk profile of the TED dose regimen.[2]

Conclusion: Teprotumumab PK was characterized in TED patients by long elimination half-life, low systemic clearance and low volume of distribution, consistent with other IgG1 mAbs. There was no meaningful exposure-response relationship at the selected TED dose regimen for both efficacy and safety endpoints, supporting the teprotumumab dose regimen used in TED patients.

Reference: (1) Smith TJ, et al. *N Engl J Med* 2017;376:1748-1761. (2) Douglas RS, et al. AACE 2019 late-breaking abstract. (3) ClinicalTrials.gov: NCT00400361. (4) Dirks NL et al. *Clin Pharmacokinet*. 2010;49(10):633-59. (5) Ryman JT et al. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(9):576-88.

Diabetes Mellitus and Glucose Metabolism

DIABETES DIAGNOSIS, TREATMENT AND COMPLICATIONS

Gender Difference in the Outcome of Patients with Diabetes Admitted for Hyperosmolar Hyperglycemia. from the National Inpatient Sample.

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SUN-620

Objective: There is paucity of literature on the impact of gender on outcomes of hyperosmolar hyperglycemic state (HHS) among adult patients with diabetes. The aim of this study was to evaluate the effect of gender on the outcome of these patients. Methodology: The National Inpatient Sample (NIS) was queried for all patients who were admitted with a diagnosis of hyperosmolar hyperglycemic state (HHS) during the years 2005-2014. The primary outcomes of the study were all-cause mortality, acute myocardial infarction (MI), and acute stroke. The secondary outcomes were acute kidney injury (AKI), rhabdomyolysis, acute respiratory failure (ARF), need for mechanical ventilation (MV), length of stay (LOS), and total cost of stay. Results: Overall, 188,725 patients were admitted for HHS. Mean age of males was 53.7, standard error of the mean (SEM: 0.13), and of females was 58.5 (SEM: 0.15), p<0.001. Females were (43.9%), Caucasians were 37.4% while African Americans were 35.2%. Total mortality was 1.1%, MI was 1.3% and stroke was 1.1%. Most common secondary outcome was AKI seen in 31.3% followed by ARF seen in 2.9% of total. The mean cost was 7887 $ (SEM: 84.6) and mean LOS was 4.1 days (SEM: 0.03). Both males and females had equivalent rates of mortality, stroke, ARF and need for mechanical ventilation. Compared to males, females had significantly higher risk for MI 1.6% vs 1.1%, p<0.001, lower risk for AKI 29.3% vs 32.9%, p<0.001, lower risk for rhabdomyolysis 1.1% vs 2%, p<0.001 and higher LOS 4.3 vs 3.9 days, p<0..01 and higher total costs 8165.6 $ vs 7669.3 $, p < 0.001. On multivariable analysis, female gender was independently predictive for higher risk for MI with adjusted odds ratio (aOR) 1.34 [95%CI: 1.08-1.67] p=0.01 and lower risk for rhabdomyolysis with aOR 0.52 [95%CI: 0.42-0.63] p<0.001 and lower risk for AKI with aOR 0.74 [95%CI: 0.7-0.78] p<0.001. In addition, female gender correlated with higher cost and length of stay. Conclusion: Females with hyperosmolar hyperglycemic state are at higher risk for MI and lower risk for AKI and rhabdomyolysis.

Healthcare Delivery and Education

EXPANDING CLINICAL CONSIDERATIONS FOR PATIENT TESTING AND CARE

Coordination of Care: National Survey of Endocrinologists' Experience with PCPs

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MON-138

Introduction:

Coordination of care between primary care physicians (PCPs) and specialists is crucial in providing safe, efficient specialty care for referred patients, but shortcomings in coordination are common.

Objective:

Examine endocrinologists' experience of coordination with PCPs and examine the relationship of a shared EHR to coordination.

Methods: