Adrenocortical carcinoma (ACC) in an aggressive malignancy with suboptimal response to frontline chemotherapy and without established second line treatment. c-MET activation is associated with ACC resistance to chemotherapy. Cabozantinib is a multi-kinase inhibitor that targets the VEGFR, c-MET, AXL, and RET receptors. We report interim data about using cabozantinib in ACC through a prospective phase II clinical trial. Methods: This is an investigator-initiated, open label clinical trial to evaluate the efficacy and safety of cabozantinib in patients with unresectable/metastatic ACC with significant reduction of parathormone levels *and* with 1,25dihydroxy-D3 (calcitriol) which were associated with significant reduction of parathormone levels *and* continued normalization of calcium levels* [as well as significant improvement in bone density.] We are instituting a long-term, double-blind, placebo controlled clinical trial - with design presented here - to determine whether or not the incidence of hypercalcemic hyperparathyroidism can be significantly reduced or even obliterated by treatment with calcitriol.

Conclusions: In this interim analysis of phase II study, majority of subjects reached the study primary endpoint (PFS4). These data are in favor of continuing study accrual to assess magnitude of response to therapy and safety profile in ACC. Aggressive blood pressure management and close monitoring of liver enzymes are crucial to ensure the safety of study subjects.

Bone and mineral metabolism

Parathyroid hormone translational and clinical aspects

Is Most “Primary” Hyperparathyroidism Both Tertiary and Preventable?

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SAT-403

Primary Hyperparathyroidism has reached epidemic proportions since the advent of mass screening for laboratory parameters including calcium. Secondary Hyperparathyroidism has been considered by some individuals as “Normocalcemic Primary Hyperparathyroidism” (4th International Workshop on The Management of Asymptomatic Primary Hyperparathyroidism, Florence, 2013 Bilzkekan et al.: “Normocalcemic PHPT is a clinical presentation of PHPT: management approach is recommended.”) We report a single case of severe secondary hyperparathyroidism (with severe osteomalacia due to ileal resection) as well as 56 subsequent secondary hyperparathyroid cases treated with 1,25dihydroxy-D3 (calcitriol) which were associated with significant reduction of parathormone levels *and* continued normalization of calcium levels* [as well as significant improvement in bone density.] We are instituting a long-term, double-blind, placebo controlled clinical trial - with design presented here - to determine whether or not the incidence of hypercalcemic hyperparathyroidism can be significantly reduced or even obliterated by treatment with calcitriol.

Mrs. K.E.
Date Ca++ PTH Calcitriol

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1997/05/01 8.5 344.0 0.25 i po qd
1997/05/28 8.5 388.0 0.25 i po qd
1997/07/21 9.3 102.0 0.50 ii po tid
1997/08/21 9.3 167.0 0.50 ii po qd
1997/11/14 10.4 11.4 0.50 ii po qd
1998/01/26 11.2 0 (!) 0.50 i po tid
1998/04/28 9.7 8.6 0.50 i po tid
1998/06/26 9.5 11.4 0.50 i po tid
1999/04/28 9.4 15.2 0.50 i po tid
2000/02/04 8.7 16.0 0.50 i po tid
2000/05/01 9.3 15.1 0.50 i po tid

Baseline Values

Statistic: Ca++ /PTH, Total: 910.70 / 4170.00, Average: 9.49/73.16, Count: 57/57, Maximum: 11.70/211.00, Minimum: 4.90 /12.00, Variance: 1.38 /73.16, SD: 2.47/59.34

Post-Treatment with Calcitriol

Statistic: Ca++ PTH, Total: 910.70/4170.00, Average: 9.49/73.16, Count: 57/57, Minimum: 4.90/12.00, Variance: 1.38/923.70, SD: 1.18/43.86
99% confidence interval around the 49.9 pg/ml difference was (-75.5 to -24.3 pg/ml).

Proposed Clinical Trial: Calcitriol to Prevent Hyperparathyroidism (CaPH) Trial

Double-blind, randomized, parallel-controlled clinical trial stratified by history of nephrolithiasis with follow-up for 5-year duration.

Calcitriol Rx to keep PTH< 70 vs Ergocalciflor to keep 25-OH D3 >30

N=100 patients/arm

Visits q90 days

Bone densitometry [including lateral spine] qyear

Telopeptides, Crosslinks, Alkaline Phosphatase, UV/

Pealcium/creatinine,Flat Plates

Exclusion: Pcreatinine>2.0 mg/dl, Ca++>10.0 mg/ dl,Familial HPTH

Inclusion: PTH >70 pg/ml

Primary Efficacy Variable: Number of documented cases of Hypercalcemic Hyperparathyroidism

Secondary Variables: Mortality, Kidney stones, Bone density, Fractures

Neuroendocrinology and Pituitary

CASE REPORTS IN CLASSICAL AND UNUSUAL CAUSES OF HYPOPITUITARISM

Hypothalamic Lipoma and Growth Hormone Deficiency

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SAT-240

Introduction: Intracranial lipomas are rare, congenital lesions, most often located at the midline. Most hypothalamic lipomas are asymptomatic, but some cases have been associated with precocious puberty, hypothermia, headache and/or obesity.

Case: A 7-year-old boy was referred for short stature, and proved to be partially growth-hormone deficient. Magnetic resonance imaging (MRI) revealed a lipoma in the paramedian hypothalamus. Growth hormone treatment resulted in swift and uncomplicated catch-up growth.

Discussion: The present case appears to be the first to link hypothalamic lipoma to GH deficiency. The neuroendocrine pathophysiology underpinning this link remains to be explored.

Reproductive Endocrinology

CLINICAL STUDIES IN FEMALE REPRODUCTION I

The Associations of Kisspeptin with Reproductive Hormones and Oocyte Maturation in Infertile Patients Who Underwent IVF Treatment

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SAT-019

Kisspeptin has been recognized as a stimulatory factor of the hypothalamic-pituitary-gonadal (HPG) axis. Kisspeptin has been successfully used to trigger ovulation in in vitro fertilization (IVF) treatment (1). This study aimed to 1) compare reproductive hormones (FSH, LH, estradiol, progesterone, and AMH), serum and follicular fluid kisspeptin between successful and unsuccessful clinical pregnancy in different stages of IVF treatment; 2) determine the correlations of serum or follicular fluid kisspeptin with reproductive hormones as well as biochemical and clinical outcomes; and 3) compare the levels of kisspeptin between serum and follicular fluid. In this study, 30 infertile female patients (age 26–40 years old) undergoing IVF treatment were recruited. Blood samples were collected at 3 different time points, the beginning of gonadotropin stimulation (the early follicular phase or T1), the scheduled day for ovum pick-up (OPU) (the late follicular phase or T2), and the day of OPU (T3). Meanwhile, biochemical and clinical parameters including the number of retrieved oocytes, matured oocytes, 2 pronuclear (2PN), and serum hCG were also determined. Moreover, fetus heart beat at 6 weeks of gestation was measured to classify the subjects into successful (n=10) and unsuccessful (n=20) clinical pregnancies. Serum AMH at T1 was significantly higher but serum FSH at T1 and T2 was significantly lower in the success group compared with the unsuccessful group (P<0.05 all). Serum kisspeptin at T2 (P=0.09) and serum estradiol at T3 (P=0.05) tended to be higher in the success group compared with non-success group. Serum kisspeptin at T1 had negative correlations with the number of retrieved oocytes (R=-0.511), matured oocytes (R=0.388), and 2PN (R=0.451) (P<0.05 all). Serum kisspeptin at T2 had positive correlations with serum LH at T2 (R=0.455), serum kisspeptin at T3 (R=0.645), the number of retrieved oocytes (R=0.465), matured oocytes (R=0.432), and 2PN (R=0.445), and serum hCG levels (R=0.438) (P<0.05 all). Serum kisspeptin at T3 had positive correlations with serum estradiol at T3 (R=0.380), the number of retrieved oocytes (R=0.601), matured oocytes (R=0.565), and 2PN (R=0.562) (P<0.05 all). Follicular fluid kisspeptin levels had a negative correlation with serum FSH at T3 (R=-0.482) but a positive correlation with the number of matured oocytes (R=0.407) (P<0.05 all). Kisspeptin levels in the follicular fluid (3.34±3.74 ng/ml) were significantly higher than in serum at T3 (0.51±0.13 mg/ml) (P<0.01).

As a result, kisspeptin at T2 was positively correlated with LH and clinical outcomes, suggesting that kisspeptin might play a role in augmentation of pre-ovulatory LH surge, improvement of oocyte maturation, and ovulation.

Thus, kisspeptin might be used as a potential predictor of successful IVF treatment. Reference: (1) Abbara A, et al. J Clin Endocrinol Metab. 2015;100(9):3322–31.

Thyroid

HPT-AXIS AND THYROID HORMONE ACTION

Transcriptome Comparison of a Natural T3, Regulated Process and a Treatment with T3.

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