

efficient blockade of the MC2R and the highest shift of EC₅₀ of ACTH (33.8 nM ± 0.08 vs. 7.3 nM ± 0.09). LNP009 was additionally tested for specificity concerning the other known melanocortin receptors and showed no antagonistic effect up to 1 μM on MC3, MC4 or MC5 receptor transiently transfected HEK 293 cells. To further investigate the inhibitory effect of our most potent antagonist peptide LNP009 on the steroid hormone response, we assessed steroidogenic enzyme expression of the human adrenocortical tumor cell line NCI-H295RA and performed mass spectrometry analyzes of steroids in the cell culture supernatant. Pre-incubation with LNP009 reduced the expression of the genes CYP21A2, CYP11B1 and HSD3B2 in NCI-H295RA cells and significantly reduced the synthesis of aldosterone (P=0.046; n=3), cortisol (P=0.020; n=3) and corticosterone (P=0.035; n=3).

With the successful blocking of the ACTH binding and signal transduction by our antagonistic peptides, we anticipate an alternative approach for optimizing the treatment of CAH patients lacking the side effects of the currently used ACTH-suppressing corticoid therapy.

Adipose Tissue, Appetite, and Obesity OBESITY TREATMENT: GUT HORMONES, DRUG THERAPY, BARIATRIC SURGERY AND DIET

The Impact of Bariatric Surgery on the Risk of Non-Alcoholic Fatty Liver Disease in Morbidly Obese Patients

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is strongly associated with obesity, and the prevalence of both diseases is increasing notably. The lack of effective treatment options for NAFLD is leading to a great consideration towards the identification of new approaches.

Aim: We aimed to evaluate the change one year after bariatric surgery of parameters of hepatic function and in the hepatic scores, *Fatty Liver Index* (FLI, predictor of hepatic steatosis), and BARD, *BMI, AST/ALT ratio and DM*, (predictor of hepatic fibrosis).

Methods: Observational retrospective cohort study in morbidly obese patients that underwent bariatric surgery between January 2010 and July 2018. We excluded patients missing hepatic function parameters before or one year after the surgical procedure. We used two linear regression models: 1) unadjusted; 2) adjusted for surgery type (gastric

sleeve, gastric band and gastric bypass), sex, age, body mass index, diabetes and dyslipidaemia.

Results: The included population (n=1955) had an average age of 43.1±10 years and 85.8% were female. We observed a relevant decrease in transaminases (pre-operative AST and ALT, 24.8±12.4 and 29.5±19.5U/L, vs 22.4 ± 11.1 and 22.2±14.7 post-operatively, respectively, p<0.01) and gamma-glutamyltransferase (36.9±35.4 vs 21.4±22.0U/L, p<0.01), and an increase in alkaline phosphatase (77.8±23.5 vs 80.8±25.4U/L, p<0.01) and total bilirubin (0.56±0.23 vs 0.68±0.24mg/dL, p<0.01). Both FLI and BARD markedly decrease one year after surgery (p<0.01). Comparing the surgical procedures, gastric sleeve was associated with a greater reduction of hepatic enzymes and of both FLI and BARD comparing with gastric band. Comparing with gastric bypass, sleeve was associated with a greater reduction of transaminases and alkaline phosphatase, but a smaller reduction of FLI and BARD.

Conclusion: Bariatric surgery is associated with a reduction of the hepatic enzymes and an improvement of FLI and BARD. Bariatric surgery may represent an effective therapeutic approach to NAFLD.

Bone and Mineral Metabolism PARATHYROID HORMONE TRANSLATIONAL AND CLINICAL ASPECTS

Baseline Characteristics from the Observational PARADIGM Registry of Patients with Chronic Hypoparathyroidism

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SAT-399

PARADIGM is an actively recruiting, prospective, observational registry (NCT01922440/EUPAS16927). The primary objective is to evaluate the safety and effectiveness of recombinant human parathyroid hormone, rhPTH(1-84), treatment in patients with chronic hypoparathyroidism

(HypoPT) under routine clinical care. The secondary objective is to characterize the clinical course of chronic HypoPT under conditions of routine clinical practice. At enrollment, registry inclusion criteria are patients having a HypoPT diagnosis >6 months and receiving conventional therapy (CT; eg, calcium supplements and active vitamin D), rhPTH(1-84) plus CT, or rhPTH(1-84). We present baseline characteristics of patients as of a June 30 2019 data cut. Baseline was defined as the value entered at the time of enrollment (Visit 1). Baseline symptom data exclude patients who initiated rhPTH(1-84) prior to enrollment (n=68) and are herein presented as two groups: those subsequently prescribed with rhPTH(1-84) after enrollment or those treated with CT. All data are summarized descriptively. Patient data from 64 centers in Europe and North America were analyzed. In the analysis population (n=737), 587 patients (79.6%) were female, 620 (84.1%) were white, and the mean (SD) age was 49.1 (16.45) years. The mean (SD) BMI was 19.3 (5.73) kg/m² and 30.0 (7.72) kg/m² in patients aged <18 (n=25) and ≥18 (n=587) years, respectively. The primary cause of HypoPT was thyroid surgery (n=547 [74.2%]; of these, 281 [60.0%] underwent surgery for thyroid cancer). Endocrinologists were the prescribing specialists for most patients (n=660 [89.6%]). Vitamin D and analogs were prescribed for 90.1% of patients (calcitriol, 74.2%, native vitamin D, 47.4%, alfacalcidol, 7.9%), calcium for 81.0% (calcium carbonate, 57.9%, calcium citrate, 27.1%), and thyroid hormones for 71.2% (levothyroxine, 73.4%; liothyronine, 5.8%). Symptoms reported at enrollment for the rhPTH(1-84) (n=66) and the CT groups (n=603), respectively, included fatigue (53.0%, 39.3%), paresthesia (48.5%, 29.2%), muscle twitching (48.5%, 21.1%), muscle cramping (40.9%, 33.0%), headaches (33.3%, 17.6%), anxiety (28.8%, 20.1%), muscle pain (28.8%, 19.2%), tetany (28.8%, 12.1%), and brain fog (27.3%, 16.3%). The baseline data for the overall population appear to be representative of patients with chronic HypoPT. Baseline data suggest that at enrollment patients prescribed rhPTH(1-84) after enrollment appear to have an increased burden of disease than patients receiving CT based on symptoms. PARADIGHM will be a valuable resource of real-world longitudinal data for patients with chronic HypoPT.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS I

Combination Immune Checkpoint Inhibitor Therapy for ACTH-Secreting Pituitary Carcinoma

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Introduction

Pituitary carcinoma is a rare yet serious entity with poor prognosis despite multimodal therapies. Cerebrospinal and/or systemic metastases are present by definition, making adjuvant systemic therapy necessary. Novel treatments are urgently needed for refractory cases. Immunotherapy with immune checkpoint inhibitors (ICI) targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death

1 (PD-1) or its ligand (PD-L1) has been a revolution in multiple malignancies. The expression of CTLA-4 and PD-L1 has been elucidated in pituitary adenomas and could be implicated in pituitary carcinomas as well. Hypophysitis is also a frequent endocrine immune-related adverse event, especially during CTLA-4 blockade (with ipilimumab) or combination ICI. However, the efficacy of ICI in the treatment of refractory pituitary tumors has yet to be established. In 2018, Lin et al. successfully treated a first case of a hypermutated aggressive ACTH-secreting pituitary carcinoma with ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) combination immunotherapy.

Clinical Case

We report a 40-year old male, diagnosed with an invasive ACTH-secreting pituitary macroadenoma in 2012, initially treated by transsphenoidal and transcranial surgery, followed by adjuvant stereotactic radiotherapy and several courses of ketoconazole. In 2017, he presented to our clinic for a recurrent Cushing's phenotype despite maximal dosing of ketoconazole. Therapy both with pasireotide and cabergoline was unable to normalize cortisol levels and a bilateral (subtotal) adrenalectomy was performed. In June 2018, he presented to our emergency department with acute diplopia due to a left abducens nerve palsy. Imaging revealed recurrent invasion of the tumor into the sella turcica and cavernous sinus, together with cerebellar and drop metastases at the cervical spine. Temozolomide (TMZ) was initiated for a total of 9 cycles. Progressive disease was observed with development of new onset right oculomotor nerve palsy after the last TMZ cycle, and persistence of elevated serum ACTH-cortisol and urinary cortisol levels, despite the absence of radiological progression. Therefore, he was started in a compassionate use setting with a combination ICI therapy with ipilimumab 3 mg/kg and nivolumab 1 mg/kg (for 4 cycles), followed by maintenance nivolumab therapy (240 mg) every two weeks. He has stable disease (both radiographically and hormonally) five months after the initiation of the immunotherapy.

Clinical Lesson(s) or Conclusion(s)

We report the second case of ACTH-secreting pituitary carcinoma treated with combination ICI therapy. The disease status of the patient is stable up until now, suggesting at least disease control by the immunotherapy. Checkpoint blockade inhibitors are a promising novel treatment modality for refractory pituitary tumors and should be further studied.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

Integrative Single-Cell Transcriptomic and Epigenomic Landscape of Mouse Anterior Pituitary Cell Types

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