patients were matched 1:3 with a control cohort based on age, gender, geographic region, and insurance type. Both assumed CAH and control cohorts had continuous coverage with at least 1 medical claim and 1 pharmacy claim in each year, 2018–2019. **Results:** Of 1,111 patients with assumed classic CAH, 778 were ≥18 years old (65% female; mean age [±SD], 43±17 years) and 333 were <18 years old (51% female; mean age [±SD], 11±4.7 years). Both adult and pediatric patients with assumed classic CAH were more likely than matched controls (adult N=2334; pediatric N=999) to experience events that could be related to chronic GC use, including infection (adult: 49.9% vs 37.3% [control]; pediatric: 49.5% vs 40.0%), weight gain (adult: 5.9% vs 2.5%; pediatric: 9.0% vs 2.6%), and moon face (adult: 44.0% vs 0.1%; pediatric: 37.8% vs 0.1%); all $P<0.01$ vs control. Adult patients were more likely than matched controls to experience acne (6.0% vs 3.6%), hirsutism (8.1% [47/508] vs 5.5% [84/1524]), and infertility (1.7% vs 0.4%); all $P<0.01$. Pediatric patients were more likely to experience pubertal development issues (10.5% vs 1.8%), acne (8.4% vs 5.1%), and advanced bone age (1.2% vs 0.1%); all $P<0.05$. **Conclusions:** Compared to matched controls, both adult and pediatric patients with assumed classic CAH had significantly more disease-related comorbidities and potential GC treatment-related conditions, indicating the challenges with current GC treatments. This study was limited by the assumed nature of classic CAH due to lack of a specific ICD code, but the combination of chronic GC use (>75% days) with the diagnosis code most likely used in these patients (adrenogenital disorder) supports the validity of this analysis.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Relacorilant With Pembrolizumab: A Phase 1b, Open-Label Study of a Selective Glucocorticoid Receptor Modulator Combined With a Checkpoint Inhibitor for Patients With Adrenocortical Carcinoma With Excess Glucocorticoid Production

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Adrenocortical carcinoma (ACC) is an aggressive cancer with poor response to chemotherapeutic and immunotherapeutic agents. About half of ACCs produce glucocorticoids (GC), and the presence of GC excess (hypercortisolism) is correlated with decreased survival in patients with ACC. The broad immunosuppressive effects of GC may contribute to the limited efficacy of immune checkpoint inhibitors, such as pembrolizumab, in these patients.

Antagonism of the glucocorticoid receptor (GR) has the potential to increase immune-related transcripts, thus promoting tumor immune response in ACC with GC excess. To test this hypothesis, we introduce a phase 1b study evaluating the combined treatment of relacorilant (CORT125134, Corcept Therapeutics) with pembrolizumab in patients with advanced ACC and hypercortisolism (NCT04373265). Relacorilant is a selective (no activity at other steroid receptors), oral GR modulator in development for Cushing syndrome and, in combination with chemotherapy, for various solid tumors. In healthy subjects, prednisone causes rapid reductions in eosinophils, lymphocytes, and osteocalcin and rapid increases in neutrophils. Relacorilant ameliorates these effects. In a phase 2 study in patients with endogenous Cushing syndrome treated with relacorilant, improvements in the signs and symptoms of GC excess were seen.

The primary objective of this study is to determine the safety and efficacy of the recommended regimen of relacorilant with pembrolizumab in patients with advanced ACC and hypercortisolism. Pembrolizumab infusion will occur on day 1 of each 21-day cycle, and relacorilant will be administered once daily, starting 3 days before the first pembrolizumab infusion. Relacorilant doses will be escalated in 100-mg increments (100 mg up to 400 mg, as tolerated). Patients will receive treatment until they experience disease progression or unacceptable toxicity.

Approximately 20 adults with confirmed advanced, unresectable and/or metastatic ACC will be enrolled. GC excess must be documented by either ACTH <10 pg/mL and serum cortisol >1.8 μg/dL after dexamethasone suppression testing (DST), or the presence of two of the following criteria: elevated urinary free cortisol; high late-night salivary cortisol; and DST cortisol >1.8 μg/dL.

Assessments will include safety, tolerability, and efficacy. Secondary objectives include a determination of the non-progression rate at 27 weeks, evaluation of progression-free survival, overall survival, duration of response, and an assessment of the effect of the combination on clinical manifestations of hypercortisolism.

This will be the first clinical study to evaluate whether GR antagonism promotes tumor response in patients with ACC and GC excess treated with checkpoint inhibitors.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Risk of Mental and Sleep Disorders After the Diagnosis of Adrenal Adenomas: A Population-Based Cohort Study

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Background: Adrenal adenomas are incidentally diagnosed in 7% of adults undergoing abdominal imaging. Mild autonomous cortisol secretion is present in 50% of adrenal adenomas, and even "nonfunctioning" adrenal adenomas demonstrate abnormal steroid profile. We aimed to 1) investigate the prevalence of mental and sleep disorders in patients with adrenal adenomas and to 2) determine the risk of mental and sleep disorders after

the diagnosis of adrenal adenoma in patients compared to the referent subjects from the same population **Methods:** Using a medical records linkage system, we identified adult patients living in the Olmsted County, MN diagnosed with an adrenal adenoma during 1995–2017. Patients with overt hormone excess were excluded. Every patient with adenoma was matched by sex and age to a referent subject from the same population. Subjects were followed until death or end of the study. Mental health related comorbidities and sleep disorders were assessed at baseline and during follow up. **Results:** Our cohort included 1004 patients with adrenal adenomas and 1004 referent subjects (58% women, median age of 63 years). Patients were more likely to smoke (70% vs 54%, p <0.001) and had a higher BMI (30 kg/m^2 vs 28 kg/m^2, p < 0.001). Within 5 years prior to the index date (diagnosis of adenoma), and after adjusting for BMI and smoking, patients demonstrated a higher prevalence of depression (Odds ratio, OR of 1.3 (CI95% 1.1–1.6), p=0.02), anxiety (OR of 1.4 (CI95% 1.1–1.8, p=0.003), substance abuse disorders (OR of 2.4 (CI 95% 1.7–3.4), p<0.001), but not insomnia (OR of 1.2 (CI95% 0.9–1.7) and sleep related breathing disorders (OR of 1.3 (CI 95% 0.9–1.7). During follow-up, starting 1 year after the diagnosis, patients demonstrated a higher risk of new onset depression (HR of 1.9, CI95%1.5–2.4), anxiety (HR of 1.5,CI95% 1.2–1.9), schizophrenia (HR of 1.7, CI95% 1.2–2.4), and substance abuse disorders (HR of 1.6, CI95% 1.2–2.0). Risk of sleep disorders 1 year after diagnosis was also high for insomnia (HR of 1.4, CI95% 1.1–1.9), sleep-related breathing disorders (HR of 1.8, CI95% 1.4–2.3), hypersomnias of central origin (HR of 2.0, CI95%1.04–3.96), parasomnias (HR of 2.4, CI95%1.2–4.7), and sleep-related movement disorders(HR of 1.9, CI95%1.3–2.6). **Conclusion:** Patients with adenomas are at increased risk for mental and sleep disorders, possibly explained by the underlying subtle cortisol secretion. Further prospective studies with an in-depth characterization of both hormonal secretion and mental/sleep disorders are needed. Reversibility or improvement of mental health and sleep disorders with adrenalectomy should be investigated.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Selective Serotonin Reuptake Inhibitors Increase Urinary Free Cortisol in Patients with Carney Complex and Primary Pigmented Nodular Adrenocortical Disease

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Primary pigmented nodular adrenocortical disease (PPNAD) is a rare cause of ACTH-independent Cushing syndrome predominantly associated with Carney Complex (CNC), a multiple endocrine neoplasia syndrome primarily caused by inactivating defects in *PRKAR1A*. PPNAD, which has neuroendocrine features, demonstrates cortisol production in response to serotonin as well as increased expression of tryptophan hydroxylase type 2, a serotonin synthesizing enzyme, and the serotonin (5-HT) receptors types 4, 6, and 7. This creates an autocrine/paracrine serotonergic regulatory loop that activates cortisol production. PPNAD can be diagnosed through a 6-day Liddle test (LT) showing a paradoxical increase of >50% from baseline in 24-h urinary free cortisol (UFC) on the 2nd day of high-dose dexamethasone administration (Day 6). Selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of serotonin and are widely used for the treatment of depression. We performed a retrospective cohort study of patients with CNC and PPNAD that underwent a LT to evaluate the effect of SSRIs on UFCs, with the hypothesis that SSRI use leads to an exaggerated increase in UFC through presumed activation of the described serotonergic regulatory loop. Of the 34 patients (4–65 y) with CNC and PPNAD that underwent a LT at our institution between 2004 and 2018, 4 took an SSRI during testing. No differences were observed between the SSRI (S) group and the non-SSRI (NS) group in baseline UFCs and the percent increase in UFC on D6. Specifically, the median (IQR) baseline UFC in the S group was 36 (13–252) mcg/24h (nl 4–56) vs 35 (13–98) mcg/24h in the NS group (*P*=0.95). The percent change in UFC was 208 (93–683)% in the S group and 185 (28–364)% in the NS group (*P*=0.89). However, there was a difference for overall UFC measurement (across days 1–6 of the LT) in the S group vs the NS group (P=0.03). Age <18 vs 18+ and sex did not have an effect on the outcomes (*P*=0.17 and *P*=0.74, respectively). Thus, we conclude that though the percent change in UFC during the LT was similar in both groups, there was a significant difference in overall UFC in the S group when compared to the NS group. These data support an effect of SSRIs and serotonin on UFC and consequently cortisol production in PPNAD. This interesting observation has to be confirmed in more patients with CNC and PPNAD to further elucidate the effects of SSRIs on cortisol production in patents with PPNAD-caused Cushing syndrome, as this may have significant diagnostic and therapeutic implications.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Significance of Discordant* Results: *between Confirmatory Tests in Diagnosis of Primary Aldosteronism

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Context: Current clinical guidelines recommend confirmation of positive result in at least one confirmatory test in the diagnosis of primary aldosteronism (PA). Clinical implication of multiple confirmatory tests has not been established, especially when patients show discordant results. **Objective:** The aim of the present study was to explore the role of two confirmatory tests in subtype diagnosis of PA.