higher than that of the other two AI subtypes (all p<0.05), although all Z-scores were still below 0. In multivariate analyses, patients were more likely to report a worse PCS score (<40) if they were women (OR: 3.3, CI 95%: 1.8–6.0), had SAI or GIAI (OR: 2.5, CI 95%: 1.4–4.3), had shorter duration of AI (<6 years) (OR: 2.0, CI 95%: 1.1–3.6), were treated with >25 mg hydrocortisone equivalent daily (OR: 2.3, CI 95%: 1.2–4.6), had more comorbidities related to GC excess (OR: 2.3, CI 95%: 1.3–4.0), reported higher financial burden due to AI (OR: 2.1, CI 95%: 1.3–3.6), and reported difficulties with AI management (OR: 2.5, CI 95%: 1.2–5.2). Women (OR: 2.1, CI 95%: 1.08–4.0), shorter duration of AI (OR: 2.4, CI 95%: 1.4–4.3), higher financial burden due to AI (OR: 2.3, CI 95%: 1.3–4.0), reporting difficulties with AI management (OR: 2.6, CI 95%: 1.4–4.9), and lack of family support during adrenal crisis (OR: 9.1, CI 95%: 2.3–33.3), were predictors of a worse MCS score (<40).
Conclusions: Patients with AI have substantially impaired QoL despite GC replacement therapy. Certain determinants of QoL are modifiable and achievable, such as avoiding GC over-replacement, offering detailed hands-on education in self-management, more comprehensive insurance coverage, and more robust domestic support. Our study calls for a multidimensional effort from patients, clinicians, and society to improve QoL in this vulnerable patient population.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Real World Mortality and Specific Causes of Death in Chronic Oral Glucocorticoid Use: A Systematic Review, Meta-Analysis and Meta-Regression

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Background: Glucocorticoids (GCs) are widely used as therapeutic agents with prevalence 0.9–3.7%, but they are associated with significant side effects. Understanding of mortality ratios and causes of death from GC use is poorly appreciated and likely to help shape future stratification of clinical practice. **Aims**: To perform a meta-analysis of all-cause and specific cause -mortality amongst chronic GC users. **Methods:** The protocol was registered in PROSPERO (CRD42017067530). Searches were undertaken of PubMed, EMBASE, CINHAL, web of science and Cochrane Central from 1966 to April 2019. The primary outcomes were proportion of death and SMR in chronic GC use patients. The meta-analysis was performed with STATA version 16.1. The I2, subgroup analysis and meta-regression were used to assess heterogeneity among included studies. **Results:** A total of 109,511 articles, were screened. One hundred eighteen articles with 128 patient cohorts containing 51,374 patients reporting mortality fulfilled the eligibility criteria and were included in the meta-analysis. SMR from seven autoimmune/inflammatory disease studies was 1.84 (95%CI 1.27,2.41) with I2 70.2 6%. The proportion of overall death was 0.12 (95% CI 0.1, .014) with I2 89.3%. The proportion of death was 0.18 (95% CI 0.13,0.24) with I2 92.0% in vasculitis diseases (40 studies), 0.10 (95% CI 0.08, 0.13) with I2 86.2% in connective tissue diseases (67 studies), 0.07 (95% CI 0.03, 0.13) with I2 88.7% in inflammatory diseases (15 studies), 0.28 (95% CI 0.21–0.37) with I2 0.0% in haematologic diseases (2 studies), and 0.06 (95% CI 0.05, 0.09) with I2 0.0% in respiratory diseases (3 studies). GC prescription reports were different across studies and led to different prediction of mortality with high heterogeneity. Proportion of death amongst a GC cumulative dose of 0.3 to 3.9 gram, 4.0 to 7.3 gram and 7.4 to 36.7 gram were 0.11 (95% CI 0.06, 0.20), 0.04 (95% CI 0.02, 0.08) and 0.16 (95% CI 0.08, 0.28), respectively. The proportion of deaths predicted by average mean dose of ≥ 5mg/d, >5–7.5 mg/d, >7.5–10 mg/d and >10–30 mg/d were 0.02 (95% CI 0.01, 0.10), 0.15 (95% CI 0.15, 0.16), 0.08 (95% CI 0.03, 0.19) and 0.14 (95% CI 0.11, 0.19), respectively. The proportion of death predicted by a maintenance dose of ≥5mg/d, >5–7.5 mg/d, >7.5–10 mg/d and >10–30 mg/d were 0.08 (95% CI 0.05, 0.13), 0.12(95% CI 0.05, 0.23), 0.11(95% CI 0.06, 0.210) and 0.12(95% CI 0.05, 0.24) respectively. The causes of death (77 studies) were cardiac (25.3%), infection (13.2%), malignancy (15.6%), respiratory failure (10.6%), active underlying disease (4.4%), cerebrovascular disease (1.1%) and thromboembolism (0.9%). **Conclusion:** This is the first meta-analysis of oral GC use and mortality from real-world clinical practice publications. Multiple factors contribute to mortality, including GC dose, duration of exposure, route, preparation, together with patient and disease-specific factors.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Real-World Evidence of Clinical Outcomes in Patients With Assumed Classic Congenital Adrenal Hyperplasia in the United States

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Background: Classic congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder, usually due to a deficiency in the 21-hydroxylase enzyme, that results in impaired cortisol synthesis and excess androgen production. Patients with classic CAH experience both disease-related features from excess androgens and treatment-related complications from the chronic, supraphysiologic use of glucocorticoids (GCs) often required for androgen control. This study was conducted to evaluate the demographics and clinical characteristics of adult and pediatric patients in the United States (US) with assumed classic CAH based on International Classification of Diseases (ICD) codes, GC prescriptions, and medical claims. **Methods:** Analyses were based on longitudinal patient-level data from the Decision Resources Group Real World Evidence repository, which links medical claims, prescription claims, and electronic health records from >300 million US patients. Data were analyzed for patients aged ≥18 years (adult) and <18 years (pediatric) with assumed classic CAH based on ICD 9/10 codes associated with "adrenogenital disorders" and whose proportion of days covered with a GC in 2018–2019 was >75%. These

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