Adrenal

THERAPEUTIC TRIALS AND PROGNOSTIC MARKERS FOR ADRENAL DISEASES

Mortality and Specific Causes of Death in Endogenous Cushing's Syndrome: A Systematic Review, Meta-Analysis and Meta-Regression

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Background: Endogenous Cushing's syndrome (CS) refers to an inappropriate hypercortisolism usually caused by either Cushing's disease (CD) or adrenal CS (ACS). CS results in significant morbidity and excess mortality if untreated. Even in treated cases there is often a significant health burden. Due to the rarity of CS (incidence ~ 1/1M population), single cohort studies have insufficient power for reporting accurate mortality data. Only one previous systematic review and meta-analysis for CS has been reported that limited its scope to the inclusion of specific CD subgroup. **Aims:** To perform a meta-analysis and meta-regression analysis of all-cause and specific cause -mortality amongst patients with benign endogenous CS. **Methods:** The protocol was registered in PROSPERO (CRD42017067530). Searches were undertaken of PubMed, EMBASE, CINHAL, web of science and Cochrane Central from start until April 2019. The primary outcomes were proportion of mortality and SMR. The meta-analysis was done with STATA version 16.1 software. The I2 test, subgroup analysis and meta-regression statistics were used to assess heterogeneity among included studies. **Results:** A total of 11,527 articles, were retrieved. 87 articles with 100 study cohorts containing 17,276 CS patients reporting mortality were included. Fifty-three study cohorts reported Cushing's disease (CD) patients, 27 study cohorts reported for adrenal CS patients and 20 studies cohorts reported on both types of CS. The overall SMR of all type CS was 2.91 (95% CI 2.41–3.68) with I2 =40.3%. The SMR for CD was 3.27 (95% CI 2.33–4.21) with I2 = 55.6%. The SMR in ACS was 1.62 (95% CI 0.08–3.16) with I2 =0.0%. The overall proportion of death in CS was 0.05 (95% CI 0.03–0.06) with I2 =51.86%; in CD was 0.04 (95% CI 0.03–0.06) with I2 = 62.7% and in ACS 0.06 (95% CI 0.04–0.11) with I2 = 40.3 %. The proportion of death during the 30-day operative period was highest before 1991 at 0.07 and decreased to 0.03 in 1991–2000 to 0.01 in 2001–2010 and zero after 2011. The causes of death reported across 64 studies were cardiac causes (24.7%), infection (14.4%), cerebrovascular diseases (9.4%), malignancy (9.0%), thromboembolism (4.2%), active disease (2.9%), and adrenal insufficiency (2.7%). **Conclusion:** CS is associated with increase in overall mortality. Advances in operative techniques and care have decreased peri-operative mortality over a 20 year period. The causes of death highlight the need for aggressive management of cardiovascular risk, prevention of thrombo-embolism, infection control and a normalised cortisol level.

Adrenal

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Results of the ADIUVO Study, the First Randomized Trial on Adjuvant Mitotane in Adrenocortical Carcinoma Patients

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Background: The ESE-ENSAT guidelines on the management of adrenocortical carcinoma (ACC) suggest adjuvant mitotane for patients at high risk of recurrence following radical surgery. This indication has a limited evidence base, lacking results from randomized controlled trials. No suggestion for or against adjuvant mitotane in low-risk patients was given, since studies did not stratify patients for prognosis. The randomized controlled study ADIUVO compared the efficacy of adjuvant mitotane treatment vs. observation in prolonging recurrence-free survival (RFS) in ACC patients at low-intermediate risk of recurrence.
Methods: The main inclusion criteria were: stage I-III ACC, R0 surgery, and Ki-67 ≤10%. Patients were randomly assigned 1:1 to adjuvant mitotane (MIT) or observation (OBS). The primary endpoint of the study was RFS. Patients who refused randomization were offered inclusion in the ADIUVO OBSERVATIONAL study. In this prospective, observational study, patients were managed as in the ADIUVO study. A total of 91 patients were enrolled in ADIUVO, 45 in the MIT and 46 in the OBS arm. Baseline characteristics of patients were perfectly matched between

the 2 arms: median age, 51 vs. 50.5 years; female, 73% vs. 67%; stage I, 20% vs. 26%; stage II, 67% vs. 63%, stage III, 13% vs. 11%; ACC secretion 44% vs. 36%; Weiss 5 vs. 5; respectively. In ADIUVO OBSERVATIONAL, 42 patients were treated with mitotane and 53 were untreated. Baseline characteristics of patients were matched between the 2 groups and with MIT and OBS groups in ADIUVO. Thus, the ADIUVO OBSERVATIONAL cohorts could be analyzed in parallel to those of ADIUVO.

Results: In the ADIUVO study, recurrences were 8 in the MIT and 11 in the OBS arm, while deaths were 2 and 5, respectively. RFS and overall survival (OS) did not significantly differ between the 2 arms. Tumor size was a predictor of RFS in multivariable analysis. In the OBS arm, the HR for recurrence was 1.321 (95%CI, 0.55–3.32, p=0.54) and HR for death 2.171 (95%CI, 0.52–12.12, p=0.29). The survival analysis in the ADIUVO OBSERVATIONAL study confirmed the findings of ADIUVO. Given the outcome of both studies, the NNT is 55.

Conclusions: ACC patients at low-intermediate risk of recurrence after surgery are a minority; however, they show a far better prognosis than expected (5-year RFS is about 75%) and do not benefit significantly from adjuvant mitotane. The results of the ADIUVO study do not support routine use of adjuvant mitotane in this subset of patients, who may thus avoid a potentially toxic treatment. This is an important step toward personalization of ACC care.

Adrenal

WIDE SPECTRUM OF TRANSLATIONAL ADRENAL RESEARCH

Effects of CRN04894, a Nonpeptide Orally Bioavailable ACTH Antagonist, on Corticosterone in Rodent Models of ACTH Excess

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CRN04894 is an orally administered nonpeptide that is a potent and selective antagonist for adrenocorticotropic hormone (ACTH) acting at the melanocortin 2 receptor (MC2R) and is currently under development for the treatment of diseases of ACTH excess such as Cushing's disease, congenital adrenal hyperplasia, and ectopic ACTH-secreting tumors. Cushing's disease results from an adenoma derived from pituitary corticotropic cells that secrete excess ACTH, whereas ectopic ACTH syndrome arises from nonpituitary ACTH secreting tumors. Congenital adrenal hyperplasia is a genetic disease that results in cortisol deficiency leading to high levels of ACTH and adrenal androgens. Each of these indications is characterized by high ACTH levels that act on MC2R expressed in the adrenal cortex to drive pathological elevations of adrenally derived steroid hormones. CRN04894 blocks the action of ACTH at MC2R, providing a potential novel treatment for these diseases. Preclinical models of chronic hypercortisolemia include implantation of ACTH-secreting pituitary tumor cells in mice and continuous administration of ACTH via subcutaneously implanted osmotic pumps in rats. These models induce features consistent with human diseases of ACTH excess including hypercortisolemia and hypertrophy of the adrenal glands. We employed both rodent models to examine the pharmacodynamic effects of CRN04894 on corticosterone levels and adrenal gland morphology. In the mouse pituitary tumor model, subcutaneous inoculation of the ACTH-secreting mouse pituitary tumor cell line, AtT-20, into immunodeficient mice resulted in formation of tumors and increased plasma ACTH and corticosterone levels. Repeated daily oral administration of CRN04894 for 14 days dose-dependently and robustly suppressed plasma corticosterone levels in mice with AtT-20 tumors. In the rat model, subcutaneous implantation of osmotic pumps delivering ACTH resulted in increased corticosterone levels, reduction in body weight, and hypertrophy of the adrenal glands after 7 days. Daily oral administration of CRN04894 over 7 days dose-dependently suppressed corticosterone levels, mitigated the effect of ACTH excess on body weight, and rescued the adrenal gland hypertrophy. These findings provide evidence that CRN04894 functions as an effective ACTH antagonist at MC2R to suppress adrenal corticosterone secretion in both mouse and rat models of ACTH excess and hypercortisolemia, thus providing a strong rationale for its potential therapeutic utility in diseases of ACTH excess. *This work was supported in part by an SBIR grant from the NIH awarded to Dr. Struthers (R43- DK115245)*

Adrenal

WIDE SPECTRUM OF TRANSLATIONAL ADRENAL RESEARCH

Genome-Wide Association Study Links Autoimmune Addison's Disease to Break of Central Tolerance

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