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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