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Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is an autosomal recessive disorder characterized by insufficient cortisol production resulting in excess adrenocorticotropic hormone (ACTH) and adrenal androgen production. Standard-of-care therapy with glucocorticoids (GC) is suboptimal due to the difficulty of balancing control of the ACTH-driven androgen excess against the serious long-term side effects associated with chronic supraphysiologic GC exposure. Tildacerfont, a second-generation corticotropin-releasing factor type-1 (CRF_1) receptor antagonist, lowers excess ACTH, and thus has the potential to reduce adrenal androgen production and to allow for GC dosing closer to physiologic doses. A prior study demonstrated that tildacerfont was effective in reducing ACTH, 17-hydroxyprogesterone (17-OHP) and androstenedione (A4) after 2 weeks of therapy. Here we report results from an open-label 12-week extension study. **Methods:** Subjects met either of the following criteria: 1) completion of prior study or 2) treatment naïve to tildacerfont with 17-OHP >800 ng/dL while on a stable GC regimen (excluding dexamethasone). Subjects were treated with oral tildacerfont at 400 mg once daily for 12 weeks. Efficacy and safety parameters were assessed at baseline through Week 12. **Results:** Subject characteristics (n=8) are as follows: median (range) age was 44.5 years (26-67 years; 5 females), median (range) body mass index 30.8 kg/m^2 (22-41 kg/m^2). In month 3, in the participants with poor control of disease at baseline (elevations in all key biomarkers: ACTH, 17-OHP, and A4) (n=5), maximum mean percentage reductions for ACTH, 17-OHP and A4 were 84%, 82%, and 79%, respectively. In this subgroup, 60% of subjects achieved ACTH normalization and 40% achieved A4 normalization during treatment. Tildacerfont treatment maintained, and did not suppress, biomarkers in participants with good control of disease at baseline (A4 below upper limit of normal) (n=3). Overall, tildacerfont was well tolerated with no serious adverse events.
Conclusions: This is the first study of 12 weeks' duration for a novel, non-steroidal mechanism-of-action agent for the treatment of 21-OHD. Results of this study show that tildacerfont was generally well-tolerated and effective in achieving meaningful reductions in ACTH and A4 in poorly controlled patients over 12 weeks. In addition, this is the first, non-steroidal therapeutic to show evidence of ACTH and A4 normalization over 12 weeks of therapy. Longer term future studies will evaluate whether treatment with tildacerfont can achieve further clinical benefits and allow reduction of GC doses while controlling relevant disease biomarkers.

Endocrine Disruption

ENDOCRINE DISRUPTING COMPOUNDS: MECHANISMS OF ACTION AND CLINICAL IMPLICATIONS

TLANDO, a Novel Oral TRT, Improves Sexual and Mental Domain Outcomes in Hypogonadal Men

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Male hypogonadism is characterized by symptoms and deficiency (<300 ng/dL) in levels of in total testosterone (TT), a critical hormone for sexual, cognitive, and body function and development. TLANDO, a testosterone undecanoate (TU) comprising lymphatically delivered oral testosterone replacement therapy (TRT) option not requiring dose titration, treatment has demonstrated effective restoration in hypogonadal men of TT levels to the eugonadal range in multiple clinical studies. TLANDO therapy resulted in decreased sex hormone binding globulin with increased free testosterone (FT). TLANDO's unique delivery system enables consistent restoration of TT regardless of meal fat content. Moreover, TLANDO has shown potential to improve liver health through resolution of fatty liver disease in hypogonadal men and is not known to have any adverse liver effects. However, it is unclear if fixed dose TLANDO therapy without dose adjustment improves symptoms of psychosexual functions. The objective is to assess key sexual and mental domain Patient Reported Outcomes (PRO) post 52 weeks of treatment using TLANDO on the to-be-marketed dosing regimen in comparison with a widely used topical TRT, Androgel 1.62%. Data analysis was performed in in hypogonadal males post TLANDO treatment without dose adjustment, and in patients on the active control from a randomized, multi-center, open label, active controlled 52-week trial (SOAR, NCT02081300). Sexual and mental domain function PROs were measured at baseline (BL) and end of study (EOS) using Psychosexual Daily Questionnaire (PDQ) and Short Form (SF)-36 surveys and compared between TLANDO and active control. Post treatment with TLANDO dosing regimen not requiring dose titration, key sexual domain function PROs at week 52 were significantly ($p<0.05$) improved from BL: positive mood (BL:4.5 vs EOS:5.1, $p<0.001$), negative mood (1.8 vs 1.4, $p<0.01$), overall sexual desire (2.5 vs 3.7, $p<0.001$), sexual activity (2.5 vs 4.0, $p<0.001$), highest pleasure with partner (2.0 vs 2.8, $p=0.06$), highest pleasure without partner (1.8 vs 2.4, $p<0.05$), weekly maintained erection (3.3 vs 4.5, $p<0.001$), and weekly full erection % (50.5% vs 68.9%, $p<0.001$). Most sexual and mental function PROs were comparable to Androgel 1.62. TLANDO therapy was well tolerated through 52 weeks of treatment exposure. In conclusion, TLANDO, a novel easy to use and prescribe

TRT not requiring dose titration, demonstrated improvement in sexual and mental PROs, a significant unmet need in hypogonadal males. Further placebo-controlled studies are warranted to better elucidate these improvements.

Endocrine Disruption

ENVIRONMENTAL ENDOCRINE DISRUPTION IN DEVELOPMENT AND DISEASE

Disruption of Estrogenic and Androgenic Bioactivities in Human Fetuses Exposed to Maternal Smoking

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Endocrine disruptors (EDs) interfere with hormonal signalling and, given that multiple developmental processes are hormone-driven, the prenatal period is a window of increased sensitivity. Maternal smoking is a real-life model of *in utero* exposure to a complex mixture of EDs. Cigarette smoke contains of >7,000 pollutants, including polycyclic aromatic hydrocarbons (PAHs), which are AhR ligands and cross-talk with the estrogen receptor (ER) system. Prenatal exposure to cigarette smoke is associated with adverse outcomes, including intrauterine growth restriction and increased risk of metabolic syndrome later in life. We aimed to evaluate ED effects associated with smoke exposure in human fetuses. Fetal tissues (plasma, n=48; placenta, n=30; liver, n=29) from elective terminations of normally progressing pregnancies, ranging from 10 to 20 gestation weeks, were collected (SAFeR and FEGO studies: REC 15/NS/0123, REC 04/S0802/21). PAHs and PAH-like compounds were extracted from placenta and fetal liver. Bioactivity levels in plasma, placenta and liver extracts were determined using ER and androgen receptor (AR) transactivation reporter gene assays. PAH burden was evaluated using the AhR-responsive DR_{hp}-CALUX assay. Smoke exposure was associated with a 1.3-fold increase in plasma estrogenic activity. The developmental trajectory of androgenic activity was altered in plasma of smoke-exposed fetuses, with significant anti-androgenic activity in older fetuses (>16 weeks of gestation). In males, plasma androgenic activity was positively associated with testes weight and anogenital distance. In contrast, placentas from smoking mothers had significantly increased androgenic potential. Furthermore, AhR-like activity was 2.9-fold higher in smoke-exposed placentas compared to controls, and 2.3-fold higher in female compared to male fetal livers. Overall, all bioactivity levels were higher in placentas compared to fetal liver. Prenatal exposure to cigarette smoke is associated with higher placental AhR activation, indicative of increased xenotoxicants burden. We also report that smoke-exposed fetuses showed increased circulating estrogenic activity and disrupted androgenic potential, across 10-20 weeks of gestation, in both fetal plasma and placenta. This demonstrates that EDs present in cigarette smoke are able to interfere with hormonal signalling and alter dynamic endocrine activity profiles, which are critical to ensure appropriate, sex-specific, development. These ED effects are likely to disturb placental function and reprogramme fetal development and thus impacting on life-long health.

Endocrine Disruption

ENVIRONMENTAL ENDOCRINE DISRUPTION IN DEVELOPMENT AND DISEASE

In Utero Exposure to 17α-Hydroxyprogesterone Caproate May Contribute to Increasing Incidence Rates of Early-Onset Cancer

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Background: 17α-hydroxyprogesterone caproate (17-OHPC) is a synthetic progestogen introduced in the 1950s to treat habitual and threatened abortion in pregnant women. Although 17-OHPC is still available (tradename Makena), little is known about its effects on health of adult offspring, and questions concerning safety and effectiveness remain. For example, progestogens have been implicated in cancer, and trends in the use of 17-OHPC in early pregnancy during the 1950s and 60s parallel increasing incidence rates of certain cancers in young adults, such as early-onset colorectal cancer, born during that time. **Methods:** We examined the effect of 17-OHPC exposure in utero on risk of cancer in adult offspring in the Child Health and Development Studies, a cohort of women receiving prenatal care between June 1959 and September 1966, with deliveries through June 1967 (n=18,751 live births excluding neonatal deaths among 14,507 mothers). Diagnosed conditions and prescribed medications were abstracted from mothers' medical records beginning 6 months prior to pregnancy through delivery. We identified mothers who received 17-OHPC (tradenames Delalutin and Proluton) in early pregnancy, defined as day 1 - 140 of gestation. Incident cancers diagnosed in offspring through 2018 were ascertained by linkage with the California Cancer Registry. **Results:** Among 18,751 live births, 954 cancers were diagnosed at ages 18 - 58 years. The most frequent cancers were breast (20.9%), cervical (10.9%), colorectal (7.1%), and prostate (5.9%) cancer and melanoma (9.2%). Although few mothers (n=181, 1.0%) received 17-OHPC in early pregnancy, in utero exposure was more common in offspring diagnosed with cancer (n=18, 1.9%) compared to those without cancer (n=163, 0.9%). Conditions indicating 17-OHPC included threatened abortion (54.0%), amnionitis (9.4%), and incompetent cervix (3.0%). 17-OHPC increased risk of any cancer in offspring (OR 2.08, 95% CI 1.27, 3.40), with particularly striking associations for colorectal (OR 4.78, 95% CI 1.49, 15.41) and prostate (OR 3.83, 95% CI 0.93, 15.83) cancer. There was no association between conditions indicating 17-OHPC and risk of any cancer in offspring (threatened abortion: n=1,891 mothers, OR 1.07, 95% CI 0.87, 1.32), or with use of other progestogens within 6 months prior to pregnancy (medroxyprogesterone acetate: n=50 mothers, OR 0.38, 95% CI 0.05, 2.76). **Conclusions:** Findings support susceptibility of multiple organ systems to endocrine disruption during early development and risk of cancer decades later - and may partly explain increasing rates of