Effect of Tildacerfont on Gonadotropins and Testicular Steroidogenesis in Men with Classic 21-hydroxylase Deficiency

Ahmed Khattab[1], R Will Charlton[2], and Richard J Auchus[3]

[1]Division of Pediatric Endocrinology, Rutgers-Robert Wood Johnson Medical School, Child Health Institute of New Jersey, New Brunswick, New Jersey, USA;

[2]Spruce Biosciences, Inc., South San Francisco, California, USA; [3] Departments of Pharmacology and Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan Medical School, USA

Background:

- Impaired testicular function is a common comorbidity of classic 21-hydroxylase deficiency congenital adrenal hyperplasia (21-OHD CAH)
- Testicular adrenal rest tumors (TART) can disrupt testicular architecture and cause primary hypogonadism
- Both supraphysiologic glucocorticoid doses and adrenal-derived androgens/estrogens can suppress gonadotropins and cause secondary hypogonadism
- An androstenedione/testosterone ratio (A4/T) of >1, in the presence of suppressed Luteinizing hormone (LH), suggests that testosterone is primarily of adrenal rather than testicular origin

Objectives:

We conducted a post-hoc analysis of gonadal axis function in men with 21OHD participating in SPR001-201 and SPR001-202, two phase 2 studies of tildacerfont, a once-daily oral corticotrophin-releasing factor receptor 1 (CRFR1) antagonist, designed to reduce ACTH mediated adrenal steroid production, including androstenedione (A4)

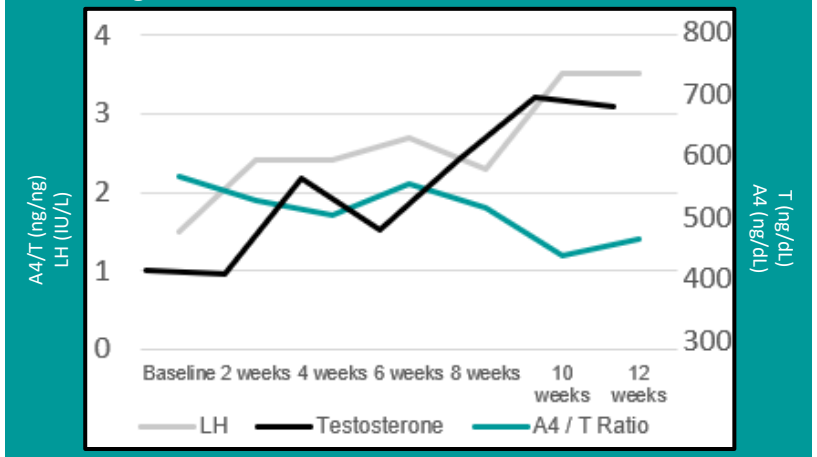
Methods:

- All male participants with adequate hormonal profiles from studies 201 and 202 were included
- Study 201 included 3 cohorts:
  - Cohort A: 5 men who received tildacerfont in a 6-wk dose escalation – 2 wks at 200 mg QD, 2 wks at 600 mg QD, and 2 wks at 1000 mg QD without washout between doses
  - Cohort B: 1 man who received tildacerfont 200 mg BID for 2 wks
  - Cohort C: 4 men who received tildacerfont 100 mg BID for 2 wks
- Study 202 included 4 men who received tildacerfont 400 mg QD for 12 wks
- Participants continued their previously prescribed glucocorticoid ± mineralocorticoid replacement without dose adjustments
- Geometric means were used to describe hormone levels due to the small participant numbers

Baseline Demographics:

- Mean and median ages were 46/32 years (Study 201) and 32/35 years (Study 202), with a range of 18-54 years
- All participants reported race as white except one who identified as white and Asian, four reported ethnicity as Hispanic or Latino

Fig 1. Combined Markers of Testicular Function



Data above from studies 201 and 202 were combined to illustrate trends
LH - Luteinizing hormone, T – Testosterone, A4/T–Androstenedione to Testosterone Ratio

Table 1. Study 201

Time (weeks)	0	2	4	6
LH (IU/L) (n)	0.68 (10)	1.59 (10)	1.62 (5)	0.85 (4)
T (ng/dL) (n)	375.5 (9)	390.5 (4)	485.4 (4)	420.7 (4)
A4/T Ratio (n)	1.28 (9)	0.59 (9)	0.87 (4)	1.03 (4)

Table 2. Study 202

Time(wks) (n)	0 (4)	2 (4)	4 (4)	6 (4)	8 (4)	10 (4)	12 (4)
LH (IU/L)	0.44	0.55	0.65	0.81	0.67	0.87	0.87
T (ng/dL)	448.4	348.9	395.8	306.0	368.0	422.5	412
A4/T Ratio	2.44	1.25	1.08	1.09	1.14	0.60	0.68

Results:

- Baseline testosterone (T) levels were normal except for four 201 participants who had T <300 ng/dL
- Baseline LH was suppressed in 6/11 (55%)
  - 4/11 (36%) had hypogonadotropic hypogonadism, low LH and T
- Baseline A4/T ratios were >1 in 11/14 (79%) subjects, indicating a predominantly adrenal origin of T
- In Study 201
  - Mean T levels increased from 375.5 ng/dL to 390.5 ng/dL at week 2 (n=9), 485.4 ng/dL at week 4 (n=4) and 420.7 ng/dL at week 6 (n=4)
  - Mean LH levels increased from 0.68 IU/L to 1.59 IU/L at week 2 (n=10), 1.62 IU/L at week 4 (n=5) and 0.85 IU/L at week 6 (n=4)
  - Mean A4/T ratios decreased from baseline of 1.28 to 0.59 at week 2 (n=9), 0.87 at week 4 (n=4), and 1.03 at week 6 (n=4)
- In Study 202
  - Mean T levels were 448.4 ng/dL at baseline and 412.0 ng/dL at week 12
  - Mean LH levels increased from 0.44 IU/L at baseline to 0.87 IU/L at week 12
  - Mean A4/T ratios decreased from baseline of 2.44 to 0.68 at week 12

Hypogonadotropic hypogonadism

- Of the four men who had low T and suppressed LH, LH rose in all 4 and normalized in 3/4 (75%)
- All the hypogonadal men experienced reductions in A4/T ratios, and 3/4 (75%) achieved A4/T <1

Conclusions:

- Gonadal axis disruption is common in men with classical 21OHD
- Modulation of adrenal androgen production via CRFR1 antagonism may improve testicular function in classical 21OHD CAH

References:

1. Auchus, Arlt, KCEM 2013
2. Engels et al, Eur J Endo 2018
3. Dudzinska et al, Int J Endo 2014