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Extended Abstract

An integrated PK-PD model for cortisol and the 17-hydroxyprogesterone and androstenedione biomarkers in children with congenital adrenal hyperplasia.

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Abstract

Patients with classic congenital adrenal hyperplasia (CAH) often require supraphysiologic glucocorticoid doses to suppress adrenocorticotropic hormone (ACTH) and control androgen excess. Nevanimibe hydrochloride (ATR-101), which selectively inhibits adrenal cortex function, might reduce androgen excess independent of ACTH and thus allow for lower glucocorticoid dosing in CAH. 17-hydroxyprogesterone (17-OHP) and androstenedione are CAH biomarkers used to monitor androgen excess.

Objective: To characterize the pharmacokinetic/pharmacodynamics relationships of cortisol and the adrenal biomarkers 17-hydroxyprogesterone and androstenedione in children with congenital adrenal hyperplasia (CAH).

Design: This was a multicentre, single-blind, dose-titration study. CAH subjects with baseline 17-OHP ≥4× the upper limit of normal (ULN) received the lowest dose of nevanimibe for 2 weeks followed by a single-blind 2-week placebo washout. Nevanimibe was gradually titrated up if the primary outcome measure (17-OHP ≤2× ULN) was not met. A total of 5 nevanimibe dose levels were possible (125, 250, 500, 750, 1000 mg twice daily). A nonlinear mixed-effect modelling approach was used to analyse cortisol, 17-hydroxyprogesterone and androstenedione concentrations obtained over six hours from children with CAH (n=50). A circadian rhythm was evident and the model leveraged literature information on circadian rhythm in untreated children with CAH. Indirect response models were applied in which cortisol inhibited the production rate of all three compounds using an I-max model.

Results: The study enrolled 10 adults: 9 completed the study, and 1 discontinued early due to a related serious adverse event. At baseline, the mean age was 30.3 ± 13.8 years, and the maintenance glucocorticoid dose, expressed as hydrocortisone equivalents, was 24.7 ± 10.4 mg/day. Two subjects met the primary endpoint, and 5 others experienced 17-OHP decreases ranging from 27% to 72% during nevanimibe treatment. The most common side effects were gastrointestinal (30%). There were no dose-related trends in adverse events. Cortisol was characterized by a one-compartment model with apparent clearance and volume of distribution estimated at 22.9L/h/70kg and 41.1L/70kg, respectively. The IC50 values of cortisol concentrations for cortisol, 17-hydroxyprogesterone, and androstenedione were estimated to be 1.36, 0.45 and 0.75ug/dL, respectively. The inhibitory effect was found to be more potent on 17OHP than D4A, and the IC50 values were higher in salt-wasting subjects than simple virilizers. Production rates of cortisol, 17-hydroxyprogesterone, and androstenedione were higher in simple-virilizer subjects. Half-lives of cortisol, 17-hydroxyprogesterone, and androstenedione were 60, 47, and 77 minutes, respectively

Conclusions: Nevanimibe decreased 17-OHP levels within 2 weeks of treatment. Larger studies of longer duration are needed to further evaluate its efficacy as add-on therapy for CAH. Rapidly changing biomarker responses to cortisol concentrations highlight that single measurements provide volatile information about a child's disease control. Our model closely captured observed cortisol, 17-hydroxyprogesterone, and androstenedione concentrations. It can be used to predict concentrations over 24 hours and allows many novel exposure metrics to be calculated, e.g., AUC, AUC-above-threshold, time-within-range, etc. Our long-range goal is to uncover dose-exposure-outcome relationships that clinicians can use in adjusting hydrocortisone dose and timing.

Keywords: congenital adrenal hyperplasia, adrenal hypertrophy, ATR-101, nevanimibe, clinical trial

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