Near- final or final height in boys with classical Congenital Adrenal Hyperplasia (CAH) treated with a combination of anti-androgen and anti-estrogen therapy: retrospective study of 11 cases

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OBJECTIVES

Final height (FH) is reduced in CAH, due either to overtreatment by Hydrocortisone therapy or to advanced epiphyseal closure linked to hyperandrogenism by Hydrocortisone therapeutic insufficiency. Pathological models show that estrogens are responsible of epiphyseal closure, aromatase being the enzyme which converts androgens, their unique substrate, into estrogens.

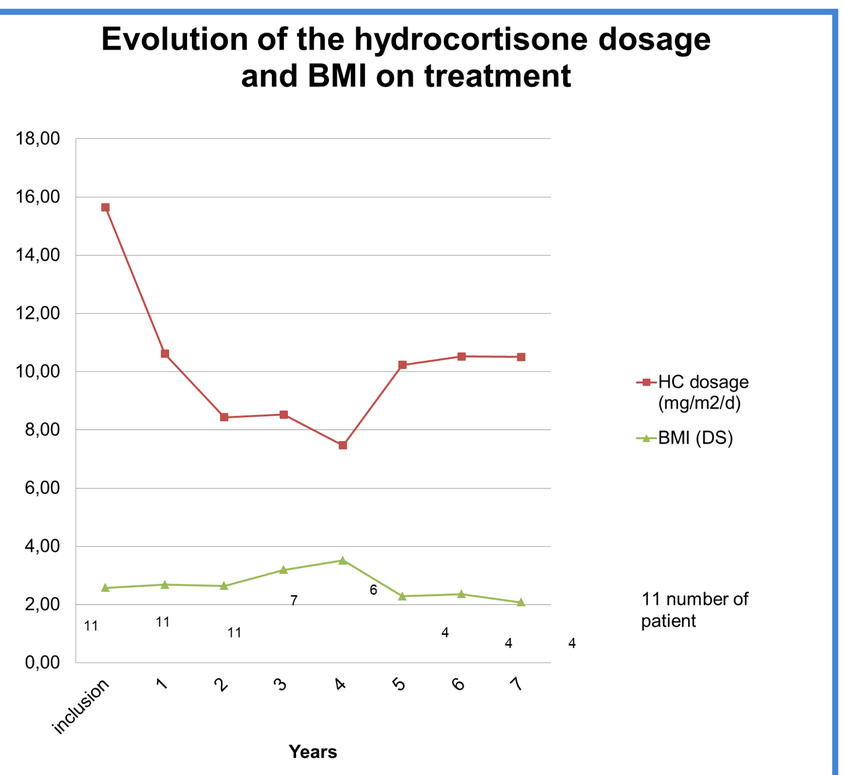
The goal of this study is to evaluate the efficacy and safety of the addition of an androgen receptor competitor and an aromatase inhibitor to reduced hydrocortisone doses.

METHODS AND POPULATION

In this retrospective study, eleven boys (chronological age 9 .4 ± 1.6 y, bone age -BA- 12.3 ± 1.6 y), with various CYP 21 gene mutations, are included because of an initial poor final height prognosis (- 1.5 ± 1.3 SDS, extreme values: 151,8 – 176,1 cm) . They were administered a treatment combining Hydrocortisone at low doses (6 mg/m^2/d instead of 15.6 ± 9.9 mg/m^2/d previously), Testolactone (40 mg/kg/d) and later Letrozole (2.5 mg/d), which are aromatase inhibitors, and Flutamide (10 mg/kg/d), an androgen receptor competitor. These additive drugs were stopped when the ratio statural age (SA) / bone age (BA) was equal to 1 or when BA was 14 years. The average chronological age at the end of the treatment was 13.2 ± 2 y. FH or near FH (NFH) were recorded.

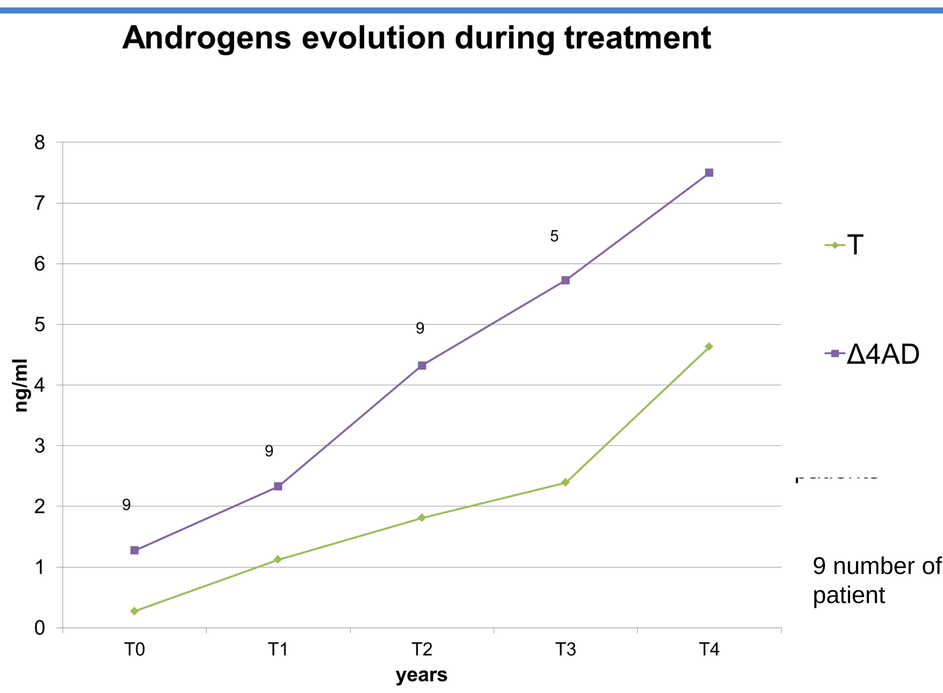
RESULTS

FH or NFH were 171.3 ± 6.6 cm (-0.7 ± 1.1 SDS). FH or NFH minus initial height prognosis was 0.9 ± 0.6 DS. No hepatic nor renal side effect were observed. Evolution of plasma ACTH levels was 116 ± 93.3 pg/ml at inclusion, 173.5 ± 158.5 pg/ml at 1 year and 132 ± 90.8 pg/ml at 2 year of the combined treatment. Hydrocortisone dose reduction did not result into any sign of adrenal insufficiency and bone mineral density remained normal in 4/11 studied patients. 6/10 patients developed testicular adrenal rest tumours. Among four patients investigated at the end of treatment, three suffered from severe semen abnormalities, one without intratesticular rests.



graph1: Evolution of the hydrocortisone dosage and BMI on treatment

Graph 2: Androgens evolution during treatment



CONCLUSIONS

It is the unique work where effective final height is observed in a treatment additioning anti-androgen and aromatase inhibiting drugs in males with classical CAH , allowing the reduction of the doses hydrocortisone. In these severely affected patients, with frequent overweight, it improved the initially poor prognosis of FH. The combined treatment can be considered as generally safe. However, we warn for a presumption of impaired fertility. Subsequent randomized studies are needed to confirm the efficiency of the additive anti-androgen and anti-estrogenic treatment in most severe CAH.

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55ESPE 49--P2

Adrenal

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DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS 10-12 SEPTEMBER