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TRANSGENDER HEALTH

Consecutive Cyproterone Acetate and Estradiol Treatment in Late-Pubertal Transgender Female Adolescents

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ABSTRACT

Background: Cyproterone acetate (CA) is an antiandrogenic progestin commonly used in adult transwomen to suppress endogenous androgens, often in combination with estrogens to induce feminization.

Aim: To assess the (side) effects and biochemical changes of CA alone and in combination with estrogens in adolescent trans-girls.

Methods: This study was a retrospective analysis of clinical and biochemical data from 27 trans-girls who presented at Tanner stage G4 and were treated with CA monotherapy for at least 6 months (mean = 12 months) and then in combination with incremental doses of estrogens (CA + E; mean = 16 months). Statistical analysis of data included paired or unpaired Student t-test or Wilcoxon signed-ranks or Mann-Whitney U-test as appropriate.

Outcomes: Anthropometrics, reported beneficial and side effects, safety parameters, and hormone levels.

Results: Physical changes included decrease of facial and non-facial hair growth. One third showed breast development under CA (Tanner stages B2–B3), which increased to Tanner stages B3 and B4 in 66.7% and 9.5% respectively, during CA + E. Reported side effects during CA and CA + E were breast tenderness, emotionality, fatigue, and flushes. No relevant weight changes were observed. Main safety parameters showed the following changes. Hemoglobin and hematocrit decreased and liver enzymes transiently and modestly increased during CA. Triglycerides and cholesterol levels slightly decreased during CA but returned to baseline during CA + E; glucose metabolism was unaffected. Relevant hormonal changes included a decrease in gonadotropins during CA + E and in total and free testosterone levels throughout treatment. Prolactin levels increased during CA and were restored during CA + E.

Clinical Implications: CA produced modest feminizing effects in trans-girls and therefore might be a valuable alternative in situations in which gonadotropin-releasing hormone analogues are not the treatment of choice and/or are not reimbursed.

Strengths and Limitations: This is the first study to report on the effects of CA in the treatment of trans-girls and one of the few to report on the use of estrogens in this population. Limitations are the modest sample size and the retrospective nature of this study.

Conclusion: Treatment with CA in late-pubertal trans-girls overall was safe and well tolerated and induced mild clinical and biochemical feminizing changes. Rapid further feminization was observed with incremental doses of E.
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Key Words: Transgender Youth; Progestins; Cyproterone Acetate; Biochemical Changes; Anthropometry; Cross-Sex Hormones

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INTRODUCTION

Gender dysphoria (GD) is defined as an incongruence between the natal and the experienced or expressed gender, which negatively affects different areas of functioning and/or entails important distress.[1] Worldwide, the number of adolescents presenting with GD is increasing.[2]

In many cases, persistent GD is already present in childhood. However, the condition will persist after the onset of puberty only in a minority of children with GD.[3] Therefore, it is recommended not to start medical therapy until the diagnosis of persistent GD is confirmed during early puberty (Tanner stages 2–3).[4] Meanwhile, psychological guidance can be offered to the child and should be continued in adolescence throughout the transition period.[5]

The goal of medical treatment is to suppress the further development of secondary sex characteristics, giving the adolescent more time to explore his or her gender identity and to decrease the extent of eventual later sex-reassignment surgery.[6] The decision to initiate medical treatment is to be made by an experienced multidisciplinary team, which in our center consists of a child psychologist, a child psychiatrist, and a pediatric endocrinologist.

In many centers, gonadotropin-releasing hormone analogues (GnRHas) are preferred as first-line therapy to suppress endogenous hormones. However, GnRHas are expensive and their beneficial effects are less clear in advanced pubertal stages, because established secondary sexual characteristics do not regress under GnRHas.[7] Another disadvantage of GnRHas in trans-girls is that, when started in early puberty, subsequent underdevelopment of the penis can compromise later penile inversion vaginoplasty.[8]

We recently reported that the androgenic progestin lynestrenol is a safe and valuable alternative for GnRHas in late-pubertal trans-boys.[9] In adult transwomen, experience has been gained with antiandrogenic progestins such as cyproterone acetate (CA) in combination with estrogens.[10] However, data are lacking for children and adolescents. CA effectively suppresses gonadotropin-independent precocious puberty and was used to suppress central precocious puberty before the advent of GnRHas.[11,12] Treatment with CA (Androcur, Bayer AG, Leverkusen, Germany) is more than five times cheaper than treatment with GnRHas, which in Belgium are not reimbursed for the treatment of transgender persons, and can be administered orally. The potent antiandrogenic effects result from its ability to competitively inhibit androgen binding on the androgen receptor, translocation of the androgen receptor to the nucleus, and inhibition of androgen-mediated transcriptional activation.[13] CA decreases growth of body hair and to a lesser extent facial hair and decreases sexual desire, which is often a cause of distress in natal boys with GD.[14,15] Because of these potent effects and the high costs of GnRHas, CA is used in our center in adolescents who already have established secondary sexual characteristics (Tanner stage $\geq$ 4) to alleviate distress before the addition of estrogens. Increases of prolactin levels and stimulatory effects on meningiomas and prolactinomas have been reported.[16,17]

According to the 2009 Endocrine Society clinical practice guideline, puberty-suppressing therapy in transgender adolescents can be associated with cross-sex hormones (CSHs) from at least 16 years of age.[18] Strict adherence to this age criterion is somewhat controversial. Adolescent-specific data on the use of estrogens in trans-girls are virtually inexistent, and guidelines are derived from studies in adults. Although estrogens alone can decrease the production of androgens in transwomen, combination with CA has been reported to be more effective in decreasing androgenic effects.[19] 17β-Estradiol (E) is the preferred estradiol, because it has a lower thrombogenic profile than ethinyl estradiol.[20–23] Based on limited evidence, estrogen-induced breast development in transwomen has been reported to be relatively modest. Possibly, breast development is more pronounced in cases in which treatment is initiated at a younger age and/or doses are increased stepwise.[24] We report on the efficacy and safety of CA alone and then in combination with estrogens in late-pubertal individuals who seek male-to-female transition.

AIM

We report on the physical and hormonal changes and the safety of treatment with CA as monotherapy and then in combination with incremental E doses in transgender female adolescents with GD.

METHODS

Patients

All trans-girls who received CA for at least 6 months from 2008 through October 2016 (N = 27) were included. The diagnosis of persistent GD was made by a child psychologist and a child psychiatrist and was based on the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* and the *International Classification of Diseases, Tenth Revision*.[7] The decision to start medical treatment was made by the multidisciplinary child gender team of Ghent University Hospital (Ghent, Belgium).

Treatment consisted of CA (Androcur) 50 mg for at least 6 months in all participants followed by a combination of CA and incremental doses of E (Progynova, Bayer AG; CA + E) in a subset (n = 21) for at least 6 months. The others were too young to be eligible for CSH therapy at the time of data analysis. Criteria to start CSH therapy were based on the Endocrine Society guidelines.[18] All adolescents were prescribed vitamin D supplementation and a calcium-enriched diet during treatment. Before the initiation of E, the adolescent and a legal guardian were asked to sign an informed assent and consent, respectively, to inform them that an off-label treatment was started, in accordance with the recommendations of our institutional ethical