ORIGINAL ARTICLE

WILEY

Exploring the efficacy of testosterone undecanoate in male children with 5α-reductase deficiency

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Funding source
Beijing Municipal Science & Technology Commission (No. Z201100005520061) and Jinlei Pediatric Endocrinology Growth Research Fund for Young Physicians (PEGRF) (No. PEGRF201809006)

Received: 21 May, 2021
Accepted: 28 September, 2021

ABSTRACT

Importance: Children with 5-alpha-reductase deficiency (5α-RD) and hypospadias present with micropenis, which makes it difficult to obtain sufficient tissue for urethral reconstruction.

Objective: We investigated the therapeutic effects of oral testosterone undecanoate and established a standard androgen treatment protocol for patients with 5α-RD with micropenis.

Methods: Patients with 5α-RD were treated with oral testosterone undecanoate for 3 months as a course. All patients were treated with no more than 3 courses. If the penile length (PL) reached 2.5 cm (the minimum criterion for surgery) or greater than or equal to −2.5 standard deviations (SDs) (lower limit of normal), testosterone undecanoate was considered to be effective.

Results: The median age of 90 patients with 5α-RD was 1.7 years (0.9, 3.1 years). The baseline PL was 1.9 ± 0.6 cm before treatment. At the end of the first course, the PL of 63 patients (70%) reached 2.5 cm, and 49 patients (54%) reached greater than or equal to −2.5 SDs. After two treatment courses, the PL of 81 patients (90%) reached 2.5 cm, and 90 patients (100%) reached greater than or equal to −2.5 SDs. After three courses, the PL of all patients reached 2.5 cm, and all patients reached a PL greater than or equal to −2.5 SDs. No abnormal increase was observed in height-SD score, weight-SD score, or ratio of bone age to chronological age during the 1–3-year follow-up.

Interpretation: After 3–9 months of treatment, PL increased to the target length. No severe adverse reactions were observed during follow-up. Testosterone undecanoate was safe and effective in children with 5α-RD with micropenis.

KEYWORDS
5α-reductase deficiency, Micropenis, Testosterone undecanoate, Treatment, Penile

INTRODUCTION

A deficiency in 5-alpha-reductase (5α-RD) is an important cause of 46, XY disorders of sex development (DSD) and is a rare autosomal recessive disorder caused by mutations in the *SRD5A2* gene encoding 5α-reductase type 2, resulting in defective conversion of testosterone to dihydrotestosterone (DHT). DHT plays a crucial role in normal male sexual development during embryogenesis and is responsible for triggering masculinization of the

DOI: 10.1002/ped4.12302

male external genitalia during early sexual development.[1,2] Patients with 5α-RD present a clinical phenotype ranging from complete feminization of the external genitalia to varying degrees of undervirilization.[1,2] Children with 5α-RD and hypospadias usually present with micropenis, which makes it difficult to obtain sufficent tissue for urethral reconstruction. Some children with 5α-RD exhibit isolated micropenis; however, they have a similar need to enlarge the size of the penis.[3]

Various mutations in *SRD5A2* lead to varying degrees of loss of enzyme activity, resulting in different testosterone to DHT conversion efficiencies. Increasing the concentration of testosterone is beneficial to the conversion to DHT. There are many clinical treatment options for 5α-RD with micropenis. The most common treatment options include DHT gel, injection of testosterone, and oral testosteron. Short-term and local application of DHT gel is safe and effective for patients with 5α-RD or other testosterone biosynthetic defects,[3] but it is expensive, and it is not available in China and many other countries. Intramuscular injection of testosterone can also increase penile size[4]; however, regimes vary considerably, and no popular protocol is available to inform the optimal dose, treatment regime, timing, and application method.[5] Injection methods are less commonly used in children, but oral testosterone treatments are effective.[6] Testosterone undecanoate is an oral testosterone preparation that is lipid soluble and absorbed directly into the lymphatic system, thereby avoiding first-pass metabolism in the liver. The androgenic activity of testosterone undecanoate occurs after the ester bond linking testosterone to undecanoic acid is cleaved by endogenous non-specific esterase. Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are DHT and estradiol. In healthy men, the plasma concentration of DHT increases with the use of testosterone undecanoate.[7,8] Testosterone and DHT act on androgen receptors in organs, thus playing an important role in promoting male growth and development of male organs and secondary sexual characteristics, as well as sustaining sexual desire.[9,10] Oral testosterone undecanoate therapy can produce a normal plasma concentration of testosterone in hypogonadal male adults and prepubertal boys. The preparation is well tolerated, and no harmful effects have been described, even after prolonged courses of therapy.[11,12]

Preoperative application of low-dose androgen in prepubertal children can effectively increase the length and diameter of the penis and stimulate the growth of penile blood vessels, thus providing a better prognosis for surgery and playing an esthetic role.[13-17] 46, XY DSDs in boys with small penises or children with severe hypospadias were treated with short-term oral testosterone undecanoate in the form of soft capsules. The results showed that oral testosterone undecanoate was effective and safe.[14,18] This study aimed to examine the therapeutic efficacy of oral testosterone undecanoate in patients with 5α-RD with micropenis and establish a standard androgen treatment protocol in these patients.

METHODS

Ethical approval

This study was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (Number: 2012-28). Written informed consent was obtained from the children's parents.

Patients

Patients diagnosed with 5α-RD from March 2009 to February 2020 were included.[19] The diagnosis was made based on the clinical characteristics, the testosterone/DHT ratio, and *SRD5A2* variants. They all carried homozygous or compound heterozygous *SRD5A2* variants that were classified as pathogenic or likely pathogenic.[19]

Inclusion criteria

The inclusion criteria were as follows: (a) a diagnosis of 5α-RD and participants' parents were determined to raise the participants as boys; (b) micropenis with concurrent hypospadias requiring preoperative androgen treatment or isolated micropenis requiring an improvement in penile length (PL) to achieve a normal appearance; (c) undergoing oral testosterone undecanoate treatment for the first time.

The participants were divided by the grading standard for hypospadias.[20] Mild concurrent hypospadias were subcoronal hypospadias (distal), moderate hypospadias were midshaft or distal penile hypospadias (mid), and severe hypospadias were scrotal or perineal hypospadias (proximal).

Exclusion criteria

The exclusion criteria were as follows: (a) previous repair of hypospadias; (b) androgen replacement therapy within 3 months before enrolment; (c) poor compliance during treatment (missed injections for more than 18 days [20% of the total 90-day treatment period] was considered poor compliance); (d) failure to follow the doctor's advice to return every 3 months for examination.

Treatment protocol

The treatment regimen was designed and modified based on a previous method for prepubertal boys with micropenis.[14,18] The dosage was 2–3 mg/(kg·d) in two or three doses via oral administration. If the effect was poor (if patients underwent 3 months of treatment, and the PL did not reach 2.5 cm [the minimum criterion for surgery] or −2.5 standard deviations [SDs; the lower limit of normal]),

treatment was continued in the next course. Other types of androgen preparation were not permitted during treatment. The course of treatment was 3 months, and afterward, the participants returned for a visit at least every 3 months. The longest treatment duration was 9 months. The dosage was adjusted appropriately according to weight, penile growth, and the main complaints of participants. For participants with hypospadias, each urologic surgeon exercised their own judgment on whether PL met their surgical conditions. Treatment was continued in some patients, even if their PL had reached the minimum required for surgery. As previously noted, urethroplasty should be performed within 2–3 months after stopping the procedure in 5α-RD patients with hypospadias.[21]

Efficacy indicators

Specialized examinations, including an increase in PL (ΔPL = PL after each course − PL before treatment), PL SD score (PL-SDS = [PL after each course − age-matched average PL in China] / [age-matched penis SD in the Chinese database]),[22] and penis diameter (PD), were measured twice by doctors at our department, and an average of the two measurements was taken. The error of the two measurements was less than 0.2 cm. The measurements were performed before inquiring about each participant's treatment history. Penis measurement was performed using the Feldman method. PL was defined as the length from the pubic symphysis to the tip of the glans with the penis stretched.

Safety indicators

The physical characteristics and general conditions of participants, including height, weight, and body mass index (BMI), were measured by professional nurses. Height SD score (height-SDS) and weight SD score (weight-SDS) were calculated according to the study of Hui et al[23] using height- and weight-standardized growth charts for Chinese children and adolescents aged 0–18 years from nine provinces and cities.

Because X-ray induces minor radiological damage and a large number of previous studies have indicated that short-term oral testosterone undecanoate has little effect on bone age,[24] we checked the bone age every 3–6 months. The bone age of participants older than 6 months was evaluated by X-ray of the left wrist with reference to the Greulich-Pyle Atlas.[25] For participants younger than 6 months of age, X-ray of the knee joint was taken to evaluate the development of epiphyseal cartilage. Routine blood and urine tests and liver and kidney function tests were performed, and the concentrations of testosterone and estradiol in serum and electrolyte, thyroid, gonadal, and adrenal hormone concentrations were measured. We also observed skin changes because it is sometimes for scrotal skin to turn black in patients using DHT cream. Patients were followed for 0.5–10 years. Long-term growth and development indicators (height-SDS, weight-SDS, BMI, and the ratio of bone age to chronological age [BA/CA]) were measured.

Statistical analysis

Statistical analysis was performed using SPSS Statistics, version 23.0. The normality was detected using the Kolmogorov-Smirnov test and presented as mean ± standard deviation. Non-normally distributed data are presented as medians and interquartile ranges. PL, PD, height, weight, and their standard deviation scores were compared before and after treatment. Data with a normal distribution were analysed using a *t*-test or repeated-measures ANOVA, and non-normal data were analysed using the Wilcoxon rank sum test. $P < 0.05$ was considered statistically significant.

RESULTS

Patients

Ninety participants were enrolled in this study. The median age of participants was 1.7 years (0.9–3.1 years). No participants were excluded because all participants demonstrated good compliance, and no participants had undergone previous androgen therapy. Twenty-four patients self-identified as being of the female gender because they possessed female external genitalia and were assigned as female at birth. After diagnosis, they were re-assigned as male and accepted treatment. Eight patients (8.9%) had mild concurrent hypospadias, 20 patients (22.2%) had moderate hypospadias, 49 patients (54.4%) had severe hypospadias, and 13 patients (14.4%) had isolated micropenis (Table 1).

Effects

The first course of treatment was completed in 90 patients. At the end of the first course, 63 participants (70%) reached the minimum criterion for surgery (PL ≥ 2.5 cm) and 49 participants (54%) reached lower limit of normal (PL ≥ −2.5 SD). However, because the urology surgeon believed some of the participants required a longer PL, 54 participants underwent a second course of treatment. After this course, 81 participants (90%) reached a PL ≥ 2.5 cm and 90 participants (100%) reached a PL ≥ −2.5 SD. Then, 21 participants underwent a third course of treatment. Finally, all participants reached a PL ≥ 2.5 cm and PL ≥ −2.5 SD (Table 1).

An increase in PL was noted compared with the data before treatment (all $P < 0.05$; Table 1). The PL before treatment was 1.9 ± 0.6 cm. At the end of the first, second, and third treatment courses, the PL was 2.8 ± 0.7 cm, 3.0 ± 0.7 cm, and 3.2 ± 0.4 cm, respectively (Table 1). However, the increase in PL varied by ≥ 10-times between participants, with maximum PL increased by 2.3 cm and minimum PL increased by 0.2 cm. The

TABLE 1 Comparison of the general condition and the effects of treatment in patients with 5α-RD

Characteristics	First course (n = 90)			First and second courses (n = 54)			All three courses (n = 21)		
	0 m	3 m	*P*	0 m	6 m	*P*	0 m	9 m	*P*
Age (years)	1.7 (0.9, 3.1)	–	–	1.3 (0.9, 2.5)	–	–	1.3 (0.9, 2.5)	–	–
Height (cm)	88.1 ± 16.9	92.8 ± 16.1	<0.001	84.6 ± 15.3	94.5 ± 14.2	<0.001	82.9 ± 9.0	98.2 ± 9.5	<0.001
Height-SDS	−0.3 ± 1.1	0.2 ± 1.2	0.001	−0.3 ± 1.2	0.5 ± 1.4	<0.001	−0.4 ± 1.6	0.7 ± 1.6	0.002
Weight (kg)	13.6 ± 5.3	15.3 ± 5.5	<0.001	12.8 ± 5.0	16.2 ± 5.8	<0.001	12.0 ± 2.5	17.4 ± 3.4	<0.001
Weight-SDS	0.1 ± 1.0	0.8 ± 1.2	<0.001	0.2 ± 1.1	1.2 ± 1.1	<0.001	0.2 ± 1.3	1.7 ± 1.4	<0.001
BMI	17.1 ± 1.9	17.5 ± 1.8	0.062	17.4 ± 2.1	17.6 ± 1.8	0.347	17.5 ± 2.6	17.8 ± 0.5	0.540
PL(cm)	1.9 ± 0.6	2.8 ± 0.7	<0.001	1.9 ± 0.6	3.0 ± 0.7	<0.001	1.6 ± 0.6	3.2 ± 0.4	<0.001
PL-SDS	−4.6 ± 1.5	−2.0 ± 1.8	<0.001	−4.8 ± 1.6	−1.8 ± 1.7	<0.001	−5.5 ± 1.6	−1.3 ± 1.1	<0.001
PD (cm)	1.0 ± 0.2	1.3 ± 0.2	<0.001	1.0 ± 0.2	1.4 ± 0.3	<0.001	1.0 ± 0.2	1.3 ± 0.3	0.001
T (ng/dL)	19.2 ± 5.9	26.8 ± 27.6	0.081	17.7 ± 7.8	29.4 ± 22.9	0.107	17.3 ± 6.5	36.7 ± 44.3	0.329
E_2 (pg/mL)	22.3 ± 10.1	23.0 ± 10.1	0.531	24.2 ± 12.1	22.3 ± 9.8	0.223	25.7 ± 10.6	26.3 ± 10.2	0.117
LH (IU/L)	0.2 (0.1, 0.3)	0.1 (0.1, 0.1)	0.003	0.2 (0.1, 0.5)	0.1 (0.1, 0.2)	0.031	0.2 (0.1, 0.5)	0.1 (0.1, 0.2)	0.162
FSH (IU/L)	0.8 (0.6, 1.2)	0.5 (0.3, 0.9)	0.019	0.8 (0.5, 1.2)	0.6 (0.3, 0.8)	0.048	0.8 (0.5, 1.2)	0.6 (0.4, 1.1)	0.071
BA/CA	1.1 ± 0.4	1.1 ± 0.3	0.695	1.1 ± 0.4	1.1 ± 0.2	0.394	1.3 ± 0.5	1.1 ± 0.1	0.297

Height-SDS, height standard deviation scores; Weight-SDS, weight standard deviation scores; m, month; BMI, body mass index; PL, penile length; PL-SDS, PL standard deviation score; PD, penile diameter; T, testosterone; E_2, estradiol; LH, luteinizing hormone; FSH, follicle stimulating hormone; BA, bone age; CA, chronological age.

penile diameter (PD) was also increased after treatment (all $P < 0.05$; Table 1).

Safety

During treatment, the participants returned for a visit every 3 months, and their height, weight, BMI, and hormone concentrations were monitored regularly (Table 1). Height, height-SDS, weight, and weight-SDS continued to increase during treatment ($P < 0.05$ for all; Table 1). The BA/CA was used to evaluate bone maturation. No significant difference was noted after treatment compared with before treatment ($P > 0.05$; Table 1). After treatment, the serum testosterone concentration increased in some patients, but still remained within in the normal range. The level of FSH and LH were decreased, but it is transient. Erectile pain was observed in one patient, but it disappeared after the dose was reduced. Two patients presented advanced bone age with accelerated growth velocity. They all reached the minimum criteria for surgery and lower limits of normal after 9 months of treatment. However, these two patients abuse the androgen for an extra 3 months without doctor's prescription. In one patient who was treated with DHT gel, before treatment, his height was equivalent to that of a healthy child, and after 3 months of DHT, his actual age was 5.5 years, his height was equivalent to that of a 6.5-year-old, and his bone age was equivalent to that of an 8-year-old. One patient was treated with testosterone undecanoate for an extra 3 months. Before treatment, his height was equivalent to that of a healthy child. After treatment, his actual age was 2.2 years, his height was equivalent to that of a 2.5-year-old, and his bone age was equivalent to that of a 4-year-old.

Serum insulin-like growth factor-1 concentration; routine blood test results; blood electrolyte concentration; glucose and lipid metabolism; and liver, kidney, and thyroid function were all within normal ranges before and after treatment, and no significant differences were observed (Table S1). All participants underwent treatment before puberty, and no participants experienced adverse reactions after treatment, such as a change in Tanner stage, growth of pubic hair, or aggressive behavior. Moreover, the scrotal skin did not turn black, and no skin pigmentation was observed.

Fifty-seven patients were followed up for more than 1 year. They showed a height-SDS of 0.7 ± 1.3 and a weight-SDS of 1.3 ± 1.4. Twenty-six patients were followed up for more than 3 years. They showed a height-SDS of 0.7 ± 1.3 and a weight-SDS of 1.3 ± 1.3. No abnormal increase in bone age was found during follow-up (Table 2). Scrotal pigmentation and brittleness were observed in two patients who intermittently applied DHT gel after surgery.

DISCUSSION

In this study, 90 patients with 5α-RD were treated with oral testosterone undecanoate. The treatment effects were evaluated by measuring PL. Most of the participants reached the criterion for surgery after 6 months of oral testosterone undecanoate treatment. All participants met

TABLE 2 Comparison of the data at the end of the treatment course and at follow-up in patients with 5α-RD

Variable	At the end of treatment	More than 1 year follow-up (n = 57)[†]	More than 3 years follow-up (n = 26)[‡]	*P1*	*P2*
Height-SDS	0.7 ± 1.6	0.7 ± 1.3	0.7 ± 1.3	0.503	0.389
Weight-SDS	1.7 ± 1.4	1.3 ± 1.4	1.3 ± 1.3	0.088	0.073
BMI	17.8 ± 0.5	17.7 ± 2.4	17.6 ± 2.3	0.858	0.973
BA/CA	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.2	0.494	0.738

[†]The median (IQR) follow up time was 2.7 (1.7–5.9) years. [‡]The median (IQR) follow up time was 4 (2.4–6.2) years. *P1*, Comparison of the data at the end of treatment and at follow-up (≥1 year). *P2*, Comparison of the data at the end of treatment and at follow-up (≥3 years). Height-SDS, height standard deviation scores; Weight-SDS, weight standard deviation scores; BMI, body mass index; BA, bone age; CA, chronological age.

the criterion for surgery and stopped after 9 months of treatment. The PL and PL-SDS gradually increased over time. After treatment, no significant difference in the growth of penile was observed at any age before puberty. Therefore, we conclude that participants can be treated at any age after diagnosis.

Our study showed that low doses of testosterone can promote penile growth However, the increase in PL in each patients differed during therapy, which may be explained as follows. First, the residual activity of the 5α-reductase enzyme differs in patients with 5α-RD; thus, patients may have different sensitivities to testosterone undecanoate.[26] Second, some children did not take the medicine with whole milk according to the doctor's recommendation. This is important because testosterone undecanoate is a lipophilic drug that has high bioavailability when taken with protein and lipid foods.

During treatment, we carefully monitored adverse reactions, such as the complications associated with testosterone overdose (rapid increase in growth promotion and bone maturation). All participants were of a short height before treatment.[27,28] We found that these participants caught up in height after treatment. Additionally, as the medication was administered over a short period, it was not possible for overgrowth to occur. Thus, short-term therapy at low doses has few adverse reactions on growth and development indices, such as height, weight, BMI, BA/CA, testosterone and estradiol concentrations, and changes in Tanner stage. However, the BA/CA and height-SDS may increase in children treated for more than 9 months, as what we found in two patients with abuse extra 3 months of drugs usage.

Although the sample size and observation indicators of this study were limited， testosterone undecanoate still showed good application prospects for the treatment of prepubertal micropenis. We will perform studies with larger sample sizes to investigate the long-term safety of this therapeutic approach.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Liu Y, Fan L, Wang X, Gong C. Exploring the efficacy of testosterone undecanoate in male children with 5α-reductase deficiency. Pediatr Investig. 2021;5:249-254. https://doi.org/10.1002/ped4.12302