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Bicalutamide as an Androgen Blocker With Secondary Effect of Promoting Feminization in Male-to-Female Transgender Adolescents

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Abstract

Purpose: The purpose of the study was to describe the novel use of bicalutamide in transgender youth.

Methods: This is a retrospective review of patients with gender dysphoria followed in the pediatric endocrine clinic at Riley Hospital for Children.

Results: Of 104 patients with gender dysphoria, 23 male-to-female adolescents received bicalutamide 50 mg daily as a second-line puberty blocker after insurance company denial of a gonadotropin-releasing hormone analog. Six patients received estrogen concurrently. Of 13 patients treated exclusively with bicalutamide seen in follow-up, 84.6% had breast development within 6 months, the majority being ≥ Tanner stage III.

Conclusions: Bicalutamide may be an alternative to gonadotropin-releasing hormone analogs in transgender male-to-female youth who are also ready to undergo physical transition.

Keywords

Bicalutamide; Transgender care; Gender dysphoria; Puberty blocker

Guidelines for the treatment of adolescents with gender dysphoria (GD) include the use of puberty blockers to suppress the reproductive system and prevent secondary sexual development contrary to the individual's affirmed gender [1]. Gonadotropin-releasing hormone analogs (GnRHas) are considered the gold standard for halting pubertal development in these youth [1]. However, insurance coverage for GnRHas for this indication varies widely. When these expensive medications are denied by third-party payers or when the copay is prohibitively expensive, other options are needed to be able to provide appropriate care for transgender adolescents. In addition to halting pubertal progression, embarking on physical transition that is aligned with gender identity is frequently expressed by patients as a goal when starting endocrine treatment [2].

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The potent androgen receptor blocker bicalutamide represents a potential alternative approach to GnRHas in natal males. Other antiandrogens used in transgender females include spironolactone and cyproterone acetate. However, both are far less potent than bicalutamide and their use has primarily been limited to adults [1,3]. In contrast, bicalutamide has been used in the treatment of familial male precocious puberty and other forms of peripheral precocious puberty in young boys [4–6]. One of the most common side effects of bicalutamide is breast development due to an alteration in the ratio of androgens to estrogens. Our experience with the use of bicalutamide in precocious puberty formed the basis for the use of this medication in male-to-female (MTF) patients with GD as a strategy for blocking puberty when GnRHas are denied. Interestingly, the resulting "side effect" of breast development has been welcomed by these patients, all of whom are eager to receive cross-hormone treatment (in this case, estrogen) and to undergo feminizing changes. We are not aware of any previous reports of utilizing bicalutamide as a way to block puberty and promote feminization in the transgender MTF population.

Methods

After institutional review board approval, medical records of patients with GD followed in the pediatric endocrine clinic at Riley Hospital for Children were reviewed. Inclusion criteria included MTF transgender patients who were treated with bicalutamide. Variables evaluated comprised age, ethnicity, duration of follow-up, timing of estrogen initiation, laboratory studies, and change in breast Tanner stage during treatment. GraphPad Prism, version 7.03, (GraphPad Software) was used for statistical analyses of sample data.

Results

Of 104 patients with GD, 39 (37.5%) were MTF patients. Of these, 23 (59%) aged 16 ± 1.77 (range 12–18.4) years were treated with bicalutamide 50 mg daily between 2013 and 2018. All but one were Caucasian. The median age when starting bicalutamide was 16.63 years. Seventeen received bicalutamide alone whereas six were started on estrogen concurrently. Fifteen patients who were started on bicalutamide alone have been seen in follow-up thus far. Of these, 1 was briefly on spironolactone and 1 was started on estrogen after 2 months on bicalutamide. Both of these patients were excluded from further analysis. The majority of the patients were prescribed bicalutamide as a second line after GnRHas were denied. However, there were some older patients who chose bicalutamide with the possible secondary feminizing effect in mind. At the first follow-up visit, which occurred at a median of 6.3 months after starting treatment, 84.6% of the patients had breast development, which ranged from Tanner stage II-V. Of the 2 patients who remained Tanner stage I, one had only been taking bicalutamide for 2 months and the other patient progressed to Tanner stage III at the second follow-up visit 12.5 months after starting bicalutamide. Thus, 100% of patients experienced breast development while on bicalutamide alone. All but 3 patients had laboratory studies obtained during the course of treatment with bicalutamide. Liver function tests (LFTs) were measured at baseline in 3 patients and between 6.3 and 29.3 months after starting bicalutamide in the remainder. Five patients had >1 set of LFTs drawn, and all were normal. Sex steroids were obtained in a subset of patients being treated exclusively with bicalutamide. Estradiol concentrations (n = 6) were <20–61 pg/dl and testosterone levels (n

= 5) ranged between 524 and 823 ng/dl. One patient had a baseline testosterone of 220.6 ng/dl which rose to 693.8 ng/dl when next measured at 14.3 months. Clinical and laboratory characteristics of patients treated with bicalutamide are summarized in Table 1. Subjectively reported effects of bicalutamide included decreased acne and reduced frequency of shaving. Anecdotally, all patients were extremely positive regarding the breast development they experienced on bicalutamide therapy.

Discussion

Bicalutamide is used in rare forms of precocious puberty in boys and has a known side effect of gynecomastia. Here, we report the novel use of bicalutamide as a puberty blocker in MTF patients with GD in whom it also results in feminization by causing breast development. To our knowledge, we are the first to report the use of bicalutamide in this setting.

We have found that bicalutamide appears to be effective in decreasing androgen exposure with the welcome side effect in these adolescents of promoting feminization. We suspect that the relatively rapid breast enlargement is because of the high potency and purely antagonistic action of bicalutamide on the androgen receptor, leading to increased testosterone levels that are subsequently aromatized to estrogen. In those tested, liver enzymes remained normal, and estradiol levels were above 20 pg/dl with only one exception. There were no apparent adverse effects of bicalutamide in our patients. However, our results must be considered extremely preliminary, and additional data are needed. How bicalutamide might compare to other androgen receptor blockers in terms of safety and efficacy in the adolescent age group is unknown, and the risk for liver toxicity needs to be investigated in larger sample sizes and over a longer duration of time.

The limitations of this study are its small size, minimal laboratory testing, and retrospective nature. Another limitation is that the efficacy of androgen suppression can only be monitored clinically, as testosterone levels actually increase. However, our results suggest that bicalutamide may be an option for transgender MTF adolescents who are denied GnRHas and are also ready for physical feminization. Bicalutamide is also significantly less costly than GnRHas, which costs thousands of dollars per dose. Larger, prospective studies with a more diverse patient population are needed to further evaluate the safety and potential role of bicalutamide in the therapeutic armamentarium for the treatment of transgender MTF youth.

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IMPLICATIONS AND CONTRIBUTION

Gonadotropin-releasing hormone analogs are often prohibitively expensive necessitating the use of alternative puberty blockers in children with gender dysphoria. This study reports on the use of bicalutamide in male-to-female youth, in whom it also causes significant feminization.

Table 1

Patients who were exclusively treated with bicalutamide who had at least one follow-up appointment

Patient number	Age of starting bicalutamide (years)	Breast development: Tanner stage at baseline	Months until first follow-up from baseline (months)	Breast development: Tanner stage at first follow-up[a]	Months until second follow-up from baseline (months)	Breast development: Tanner stage at second follow-up[a]	LFTs[b]	Estradiol[a] (pg/ml)	Testosterone[a] (ng/dL)
1	16.6	I	8.00	III			Normal	31	823
2	18.4	I	6.07	III			Normal	48	524
3	16.0	I	4.00	III			Normal	-	-
4[c]	12.0	I	7.30	II	13.3	II	-	-	-
5	16.3	I	7.23	III			Normal	26	619
6[c]	15.4	I	6.53	III	13.3	IV	-	-	-
7[c]	13.5	I	6.30	I	12.5	III	Normal	61	-
8	16.8	I	3.97	V			Normal	-	-
9[c]	17.4	I	6.97	II (Left), III (Right)	10.9	II (Left), III (Right)	Normal	-	-
10	14.6	I	7.03	IV (Left), III (Right)			-	-	-
11	16.9	I	6.30	III			Normal	34	543
12[c]	13.3	I	6.30	III	12.9	III	Normal	<20	693.8
13	18.2	I	2.17	I			Normal	-	-

[a] While exclusively on bicalutamide.

[b] While taking bicalutamide with or without concurrent estrogen.

[c] Patient had two follow-up visits while remaining exclusively on bicalutamide.