ORIGINAL ARTICLE: ANDROLOGY

Outcomes of anastrozole in oligozoospermic hypoandrogenic subfertile men

Ohad Shoshany, M.D.,[a] Nikita Abhyankar, M.D.,[a] Naem Mufarreh, M.S.,[b] Garvey Daniel, M.D.,[a] and Craig Niederberger, M.D.[a]

[a] Department of Urology, University of Illinois at Chicago, Chicago; and [b] Loyola University, Chicago, Illinois

Objective: To determine whether the change in sperm parameters in subfertile hypoandrogenic men treated with anastrozole is correlated to the magnitude of increase in testosterone (T) to estrogen ratio in men responding to treatment.
Design: Retrospective study.
Setting: Male fertility clinic.
Patient(s): The study group consisted of 86 subfertile hypoandrogenic men with low T/estradiol (E_2) ratio (n = 78) or a prior aversive reaction to clomiphene citrate (n = 8).
Intervention(s): All patients were treated with 1 mg anastrozole daily, administered orally.
Main Outcome Measure(s): Hormone analysis and semen analysis before and after treatment were performed. Hormone analysis included measurements of total T, E_2, sex-hormone binding globulin, albumin, FSH, and LH, and bioavailable T was calculated. Total motile sperm count was calculated from the semen analysis.
Result(s): In all, 95.3% of patients had an increased serum T and decreased serum E_2 after treatment with anastrozole. Sperm concentration and total motile counts improved in 18 of 21 subfertile hypoandrogenic oligozoospermic men treated with anastrozole. In these men the magnitude of total motile count increase was significantly correlated with the change in the T/E_2 ratio. No improvement was seen in semen parameters of men with azoospermia, cryptozoospermia, or normozoospermia at presentation.
Conclusion(s): Approximately 95% of men with hypoandrogenism responded with improved endocrine parameters, and a subset of oligozoospermic men (approximately 25% of all patients) displayed significantly improved sperm parameters. In that subset, increase in sperm parameters was correlated with the change in the T/E_2 ratio, which argues for a physiologic effect of treatment. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Anastrozole, aromatase inhibitors, male infertility, oligozoospermia, testosterone to estradiol ratio

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/13461-22959

Infertility affects 15% of all couples trying to conceive, and a male factor is involved in approximately 50% of these couples (1). Overall, 20% of all men undergoing an infertility evaluation will be diagnosed with an endocrine abnormality (1). The prevalence of hypoandrogenism in men with oligozoospermia, as defined by the World Health Organization (version 4), has been observed to be approximately 43% (2). This is similar to the prevalence of 45% in men with azoospermia due to spermatogenic dysfunction. In men with obstructive azoospermia, however, hypoandrogenism has a much lower incidence of approximately 16.7%, similar to that in the general population (2). Spermatogenesis is highly dependent on intratesticular testosterone (T) synthesis, and hypoandrogenism may result in a defective spermatogenesis (3). Nonetheless, hypoandrogenism is imperfectly correlated with semen parameters (4), and delineation of the subgroup of patients that would benefit from correction of hormonal abnormalities is needed.

Estrogen (E) has a role in male fertility, although it is incompletely understood. It is known to be important for normal spermatogenesis (5, 6), but high concentrations of E, perhaps combined with low concentrations of T, may be detrimental to spermatogenesis (7). Estrogen is produced by the enzyme aromatase, which converts T into estradiol (E_2) and androstenedione into estrone. Aromatase is a cytochrome P450 enzyme that is present in both the testicular germ cells and somatic

Received August 20, 2016; revised October 21, 2016; accepted November 19, 2016.
C.N. reports that he is journal editor for the American Society for Reproductive Medicine; section editor in the journal for the American Urological Association; is doing a scientific study/trial for Ferring; and is co-founder and Chief Technology Officer of NexHand. O.S. has nothing to disclose. N.A. has nothing to disclose. N.M. has nothing to disclose. G.D. has nothing to disclose.
Reprint requests: Ohad Shoshany, M.D., Department of Urology, University of Illinois at Chicago, 820 S Wood Street, Chicago, Illinois 60612 (E-mail: ohadsh10@gmail.com).

Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.11.021

cells, as well as in other tissues and organs, such as adipose tissue, liver, and brain (8, 9).

Selective E receptor modulators and aromatase inhibitors are frequently used as treatment in hypoandrogenic men desiring fertility. Anastrozole has been demonstrated to increase T concentrations and the T/E ratio (9). A small but growing number of studies support the efficacy of aromatase inhibition in the treatment of hypoandrogenic subfertile men (10–14). We aimed to assess the efficacy of anastrozole use in hypoandrogenic men by investigating whether a correlation exists between semen analysis changes and hormonal changes during treatment.

MATERIALS AND METHODS

Institutional review board approval was obtained. Hypoandrogenic subfertile men treated with anastrozole (1 mg daily) between January 2010 and May 2016 were included in this study. All patients were seen by one treating physician (C.N.) at a single male infertility center. Indications for anastrozole treatment included a low calculated bioavailable T (<155 ng/dL) and either a T (in ng/dL) to E (in pg/mL) ratio of <10 (n = 78) or a history of prior adverse reaction to clomiphene citrate (CC) (n = 8). Exclusion criteria were men with a history of sex chromosome disorder, past exogenous T use, or other concomitant hormonal treatment.

Data on demographics, medical history, physical examination, testicular longitudinal axis, side effects and adverse events, laboratory values, and semen analyses before and after treatment were collected. Hormone concentrations were assessed before treatment and at 3 weeks and 4 months after prescribing anastrozole. Hormonal analysis was obtained between 7:00 and 11:00 AM by venipuncture. Assays of sex hormone–binding globulin, E, albumin, FSH, LH, and total T were obtained at the University of Illinois at Chicago laboratory. Testosterone was measured by the quantitative electrochemiluminescent immunoassay. Estradiol was measured by quantitative high-performance liquid chromatography–tandem mass spectrometry. Bioavailable T was calculated according to the Vermeulen formula (15). Semen analyses were performed before treatment and at 4 months after treatment. Semen samples were collected by masturbation after 2 to 3 days of sexual abstinence and processed within 1 hour of ejaculation. All patients had two or more recent semen analyses before treatment, no longer than 6 months before treatment commencement. The semen analysis with the greatest total motile count was selected to represent pretreatment status. At least two centrifuged semen analyses were carefully examined before the diagnosis of azoospermia and cryptozoospermia. Side effects were recorded, and anastrozole was discontinued in cases of significant adverse events. Microsurgical testicular sperm extraction outcomes after treatment were also recorded.

For statistical analysis, variables are presented as median and interquartile range or mean ± SE, as appropriate. A matched-pairs analysis estimated significance of change in laboratory values and semen analyses with treatment. A subgroup analysis was performed of men with baseline oligozoospermia. In this group we used linear regression to identify correlations between changes in hormone concentrations and increase in semen parameters. We then used multiple regression analysis to control for age and FSH as possible confounders. Statistical tests were two-sided and were considered statistically significant when $P<.05$. Analyses were performed with IBM SPSS statistics, version 20.

RESULTS

A total of 86 men with a median age of 37 (32–41) years were included. The median duration of unprotected intercourse was 24 (18–48) months. In all, 28 patients (32.6%) were azoospermic, and 8 (9.3%) had cryptozoospermia. A history of cryptorchidism was reported by 11 patients. Four patients had a history of varicocelectomy (three oligozoospermic patients and one normozoospermic patient). Four patients had a non–clinically significant grade 1 varicocele at presentation, as they were associated with either normozoospermia or azoospermia. Mean testis longitudinal axis was 4.32 ± 0.09 cm bilaterally.

Three weeks after anastrozole was prescribed, T and bioavailable T increased from 258.4 ± 10.8 ng/dL and 128.8 ± 4.7 ng/dL to 509.2 ± 20.4 ng/dL and 297.5 ± 12.7 ng/dL, respectively (both $P<.0001$; Table 1). Estradiol concentrations decreased from 40.8 ± 1.9 pg/mL to 24.6 ± 2.1 pg/mL after 3 weeks of anastrozole treatment ($P<.0001$). The T/E_2 ratio significantly increased from 6.98 ± 0.33 to 34.5 ± 6.5 (Table 1). Over the 4 months of treatment, LH increased from 6.41 ± 0.89 IU/L to 10.7 ± 1.1 IU/L ($P<.0001$), and

TABLE 1

Hormonal analysis in 86 men with hypoandrogenism treated with anastrozole.

Parameter	Baseline	At 3 wk	At 4 mo	*P* value[a]
Total T (ng/dL)	258.4 ± 10.8	509.2 ± 20.4	449.9 ± 19.5	<.0001
Bioavailable T (ng/dL)	128.8 ± 4.7	297.5 ± 12.7	N/A	<.0001
E_2 (pg/mL)	40.8 ± 1.9	24.6 ± 2.1	23.2 ± 2.2	<.0001
T/E_2 ratio	6.98 ± 0.33	34.5 ± 6.5	24.2 ± 3	<.0001
SHBG (nmol/L)	25.6 ± 1.1	24.9 ± 1.2	N/A	NS
LH (IU/L)	6.41 ± 0.89	10.7 ± 1.1	N/A	<.0001
FSH (IU/L)	12.4 ± 2	19.4 ± 2.3	N/A	<.0001

Note: Values are mean ± SE. SHBG = sex hormone–binding globulin.
[a] Comparing baseline vs. 3-wk results.

Shoshany. Anastrozole for subfertile men. Fertil Steril 2016.