Coadministration of Anastrozole Sustains Therapeutic Testosterone Levels in Hypogonadal Men Undergoing Testosterone Pellet Insertion

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DOI: 10.1111/jsm.12320

ABSTRACT

Introduction. Current U.S. Food and Drug Administration–approved therapies for hypogonadism involve testosterone (T) replacement. Testosterone pellets (TP) require a minor office procedure every 3 to 4 months. The need for repeated insertions increases the likelihood of a complication. Anastrozole (AZ) is an aromatase inhibitor that has been used off-label for the treatment of male hypogonadism. AZ increases T levels by lowering serum estradiol (E2) levels and increasing gonadotropin (GTP) levels.

Aim. We hypothesized that the concomitant use of AZ with TP insertions would sustain therapeutic T levels and increase the interval between TP insertions.

Methods. Men treated with TP for hypogonadism at an academic center were offered AZ (1 mg/day) at the time of TP reinsertion as a way of potentially decreasing the frequency of TP insertions. Total T (TT), free T (FT), sex hormone binding globulin, E2, luteinizing hormone (LH), and follicle-stimulating hormone FSH levels were obtained prior to T replacement and at 6 and 15 weeks from TP insertion. Men were re-implanted at 16 weeks if their TT levels were less than 350 ng/dL and their symptoms recurred. We retrospectively reviewed our records of men who underwent TP, TP, and AZ from 2011 to 2012. Demographics, TT, FT, LH, FSH, and E2 levels were recorded. Data were analyzed with ANOVA and a Tukey's test.

Main Outcome Measure. TT level at 6, 15, or >15 weeks from TP insertion.

Results. Thirty-eight men with 65 insertions were analyzed. The TP AZ group had significantly higher TT and FT levels than the TP group at >120 days ($P < 0.05$). The TP group had significantly higher E2 levels at all time points ($P < 0.01$). GTP levels remained stable in the TP AZ group. Average time to reinsertion in TP AZ was 198 days vs. 128 days in the TP group.

Conclusion. Men on TP AZ maintain therapeutic T levels longer than men on TP alone and have significantly less GTP suppression. **Mechlin CW, Frankel J, and McCullough A. Coadministration of anastrozole sustains therapeutic testosterone levels in hypogonadal men undergoing testosterone pellet insertion. J Sex Med 2014;11:254–261.**

Key Words. Testosterone Pellets; Aromatase Inhibitor; Hypogonadism; Testosterone Deficiency Syndrome

Introduction

The overall prevalence of symptomatic hypogonadism is 5.6% in men aged 30–79 years and in longitudinal studies increases 1.5–2% per year after age 40 [1]. Testosterone (T) deficiency is a lifelong problem. Endocrine guidelines recommend T replacement in symptomatic men to induce and maintain sexual function, a sense of well-being, muscle mass and strength, and bone mineral density [2]. All U.S. Food and Drug Administration (U.S. FDA)–approved treatment modalities involve T replacement with injections, transdermal gels or patches, buccal lozenges, or long-acting T pellets (TP).

TP were U.S. FDA approved in 1972 and are crystalline TP that are subcutaneously implanted and enter systemic circulation through diffusion

[3]. TP have a predictable decay curve, provide sustained therapeutic T levels, and may reduce noncompliance [4–7]. The average time to re-implantation is 3–4 months after which time T levels return to pretreatment values [5,7]. TP involve an office procedure with a small risk of bleeding, infection, pain at the implant site, and extrusion [5,7]. This treatment also is associated with suppression of gonadotropins (GTPs) [4]. Prolonged exogenous suppression of testicular function often leads to testicular atrophy. GTP suppression appears to be largely mediated through the peripheral and central aromatization of T to serum estradiol E2 that occurs with exogenous T supplementation [8,9].

The pituitary gland secretes luteinizing hormone (LH), which stimulates Leydig cells in the testes to secrete T [8]. GTP-releasing hormone stimulates the pituitary to release both LH and follicle-stimulating hormone (FSH). T and estrogen exert direct negative feedback at both the pituitary and hypothalamic level [8,10]. T is peripherally and centrally converted to E2 by aromatase [9]. E2 has a potent negative effect on T production and is the main regulator of FSH secretion [11,12]. The negative feedback of estrogens can either be blocked at the receptor level or by preventing the breakdown of T to estrogens by aromatase [8].

Aromatase inhibitors (AI) were U.S. FDA approved for use in women in 1996 and have been studied in infertile, obese, and elderly hypogonadal men. Two randomized double-blind placebo-controlled trials by Leder et al. showed a significant increase in T levels in elderly men on 1 mg of anastrozole (AZ) daily [13,14]. The average total T (TT) levels increased from 323–343 (mg/dL) to 525–572 at 3 months. Letrozole was prospectively studied in 27 infertile men at a dose of 2.5 mg daily for 6 months. The average T level increased from 255 to 527 by 3 months [15]. Similar results with letrozole were seen in a recent prospective study by Gregoriou et al. [16]. Raman and Schlegel retrospectively reviewed the efficacy of testolactone or AZ on T levels in 140 infertile men. Average T levels increased from 277 to 411 and 295 to 445 in the testolactone and AZ groups, respectively [17]. There is good evidence to show that AIs significantly increase T levels in men.

There are two previous studies that have investigated the use of AIs in combination with depot-testosterone supplementation. Both of these studies were performed in a select group of men with epilepsy. The initial retrospective study included 17 hypogonadal men treated with depot-T alone or with the steroidal AI testolactone [18]. Although bioactive T (BAT) levels were not different between groups the combination group had higher sexual function scores (Brief Sexual Function Score) and lower estrogen levels. In 2010, Herzog et al. reported the results of a randomized placebo-controlled trial (RPCT) in 37 hypogonadal epileptic men treated either with depot-T alone or in combination with AZ [19]. They found that normalization of sexual interest and function scores occurred with a greater frequency in the combination group. These men had higher T to estrogen ratios but BAT levels were not significantly different between groups.

To our knowledge combination therapy with AIs and long acting TPs has not been previously reported, nor has the use of AIs with exogenous T in men without epilepsy been reported. We hypothesized that adding AZ to TP treatment would prolong therapeutic T levels. This might decrease the frequency of reinsertion and the overall morbidity over a lifetime of TP insertions.

Methods

Starting in May 2011 symptomatic hypogonadal men (T < 350 ng/dL) previously treated with TP (TP group) in our clinic were offered AZ (1 mg PO daily)(manufactured by AstroZeneca in London, UK) in addition to TP (TP AZ group) at their reinsertion visit in an attempt to prolong therapeutic T levels (>350 ng/dL). Each men received 10 pellets (75 mg per pellet) (manufactured by Slate Pharmaceuticals, Durham, North Carolina, USA). TPs were inserted in a single track in the gluteal region with the patient in the prone position. Patients were counseled that AIs were not U.S. FDA approved for the treatment of male hypogonadism but have been found to be well tolerated and effective in increasing T levels in published studies. Their mechanism of action was explained, and patients were counseled regarding possible side effects including rashes, diarrhea, headaches, joint pain, and changes in liver function enzymes.

TT, free T (FT), LH, FSH, sex hormone binding globulin (SHBG), and E2 levels were routinely obtained prior to T replacement and then at approximately 6 weeks and 4 months from treatment. Reinsertion was predicated on T levels and symptoms of hypogonadism. After institutional review board approval records were