Anastrozole single-dose protocol in women with oligo- or anovulatory infertility: results of a randomized phase II dose–response study

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Objective: To compare the effects of anastrozole and clomiphene citrate (CC) on follicular development and ovulation in infertile women with ovulatory dysfunction.
Design: Phase II, prospective, randomized, assessor-blind, multicenter, dose-finding, noninferiority study.
Setting: Outpatient.
Patient(s): Infertile women with ovulatory dysfunction, aged 18–35 years, and body mass index <35 kg/m^2.
Intervention(s): Single-dose anastrozole at 5 mg (n = 39), 10 mg (n = 39), 20 mg (n = 39), or 30 mg (n = 38) or a 5-day course of CC at 50 mg/d (n = 39) as starting doses.
Main Outcome Measure(s): The primary endpoint was the ovulation rate in the first treatment cycle (cycle 1). Ovulation was defined as a midluteal phase serum P level ≥10 ng/mL or clinical pregnancy.
Result(s): In cycle 1 the ovulation rates for a single dose of anastrozole at 5, 10, 20, and 30 mg were 46.2%, 41.0%, 23.1%, and 28.9%, respectively, whereas that for CC at 50 mg/d was 61.5%. Among women with fewer than six menses per year, the cumulative ovulation rates over three cycles were comparable in the anastrozole 5 mg (52.4%) and CC 50 mg/d (42.3%) groups.
Conclusion(s): In terms of ovulation rates in cycle 1, single-dose anastrozole at 5, 10, 20, and 30 mg was not as effective as CC at 50 mg/d for 5 days (noninferiority was not shown). (Fertil Steril® 2011;95:1725–9. ©2011 by American Society for Reproductive Medicine.)

Key Words: Anastrozole, aromatase inhibitor, clinical pregnancy, clomiphene citrate, ovulation, ovulatory dysfunction

Ovulatory disorders account for approximately 30% of infertility cases (1). Clomiphene citrate (CC) is an antiestrogen used as first-line therapy for ovulation induction for women with ovulatory dysfunction (2). Clomiphene citrate blocks hypothalamic and pituitary estrogen receptors, resulting in compensatory release of gonadotropins and ovulation (2). Approximately 70% of group II anovulatory patients ovulate after CC treatment, and approximately half of these women will achieve a pregnancy within three cycles (2). Clomiphene citrate induces peripheral antiestrogenic effects, such as suppressed production of cervical mucus and reduced endometrial proliferation, and may be detrimental to oocyte maturation (2–5). These adverse effects may contribute to the observed discrepancy between ovulation and pregnancy rates in women treated with CC (2).

Aromatase inhibitors, such as anastrozole and letrozole, have been suggested as alternatives to CC. Aromatase inhibitors block the aromatase enzyme, which suppresses estrogen production (6). Because aromatase inhibitors do not disrupt estrogen binding, the deleterious effects associated with CC may be avoided (7). Other potential benefits of anastrozole include no significant accumulation in the blood (8) and a shorter half-life than CC (9). Furthermore, there is no evidence of teratogenicity in animal studies (10) or of disruption of mitotic maturation (11) with anastrozole. Anastrozole has been effective in inducing ovulation and pregnancy in anovulatory women (12) and improving ovarian response to FSH in poor responders (13).

Single-dose letrozole has been shown to be comparable to a 5-day letrozole regimen in terms of ovarian stimulation in infertile women (14). The objective of this study was to compare single-dose anastrozole with multiple-dose CC in terms of follicular development and ovulation in infertile women with ovulatory dysfunction.

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MATERIALS AND METHODS

Study Design

This was a phase II, prospective, randomized, assessor-blind, multicenter, dose-finding, noninferiority study of single-dose anastrozole vs. multiple-dose CC (study 23963, EMD Serono, Inc., Rockland, MA). The study was conducted at 23 clinical trial sites in the United States. Institutional review board or independent ethics committee approvals were obtained at each center, and the study was conducted according to the Declaration of Helsinki and the standards of good clinical practice. All patients provided written informed consent.

Patients

Women with ovulatory dysfunction desiring pregnancy, aged 18–35 years (inclusive), with a body mass index (BMI) <35 kg/m^2, two patent fallopian tubes, and two functional ovaries were recruited. Ovulatory dysfunction was

defined as a cycle length <21 or >35 days with six or more menses per year, or cycle length >35 days with fewer than six menses per year. A positive P challenge within 6 months of study entry was required for patients in the latter group. Patients were screened during the menstrual cycle before the anticipated start of treatment.

Patients were included if they smoked no or fewer than five cigarettes per day, had no previous gonadotropin treatments, and had a male partner with a minimum sperm count of 20×10^6/mL in addition to meeting the center's minimum standards for IUI associated with ovulation induction. Exclusion criteria included having any medical condition that could interfere with the menstrual cycle or absorption, distribution, metabolism, or excretion of the study drug, three or more consecutive pregnancy losses, a residual ovarian cyst >25 mm in diameter, or more than six prior CC cycles or six nonovulatory CC cycles. Patients were specifically excluded if central laboratory screening indicated the presence of hyperandrogenism (DHEAS $\geq$7 μg/mL or T $\geq$200 ng/mL). Patients with polycystic ovary syndrome, as defined by the investigator, were included and formed 51% of the population.

Patients were randomly assigned to one of five treatment groups. In the first treatment cycle (cycle 1), patients received a single dose of anastrozole (Arimidex; AstraZeneca UK, Macclesfield, United Kingdom) at 5, 10, 20, or 30 mg or CC (Serophene; TEVA Pharmaceuticals, Petach Tikva, Israel) at 50 mg/d for 5 consecutive days. Randomization numbers were computer generated; the randomization system was not accessed by the investigator.

Treatment was initiated on day 2–3 of menses and was discontinued if an ovarian cyst >25 mm in diameter persisted after one rest cycle (without therapy for 1 month), a risk of ovarian hyperstimulation syndrome (OHSS), or World Health Organization grade 3 or 4 toxicity occurred. Serum E_2 levels were measured and a transvaginal ultrasound scan (TVUS) performed on cycle days 5–6 and 8–9. Patients with a baseline serum E_2 level >100 pg/mL were excluded from the study. The tests were repeated until a lead follicle reached 14 mm in diameter and an LH surge was detected. The use of exogenous hCG to induce ovulation was not permitted.

Insemination by sexual intercourse or IUI occurred within 24 hours of the LH surge. Midluteal phase serum P levels were measured to detect ovulation ($\geq$10 ng/mL was indicative of ovulation), and a TVUS assessed follicular details and endometrial thickness. For ovulatory patients, a serum pregnancy test was performed between days 15 and 18 after LH surge. Patients with a positive pregnancy test result (β-hCG level >10 IU/L) had the test repeated within 2–4 days, and a confirmatory TVUS was carried out between 35 and 42 days after LH surge.

If a pregnancy was not achieved in cycle 1, two further cycles were permitted; doses were adjusted according to the number of mature follicles and clinical outcome. Sexual intercourse or IUI was disallowed in patients with excessive response (four or more follicles $\geq$17 mm in diameter with or without ovulation). For patients treated with anastrozole, the dose was not changed if ovulation occurred without pregnancy (adequate response), but was decreased or stopped (depending on the dose) in patients with excessive response. The dose was increased or stopped in patients with no response. For patients receiving CC at 50 mg/d, the dose was increased to 100 mg/d if there was no response but was stopped if the response was excessive. Excessive or no response to CC at 100 mg/d resulted in treatment cessation.

Assessments and Analyses

The primary endpoint was the ovulation rate (ovulation defined as a midluteal phase serum P level $\geq$10 ng/mL or clinical pregnancy) in cycle 1. A noninferior anastrozole dose was defined as a dose that was at least as effective as CC in the induction of ovulation (i.e., if the lower bound of the 90% confidence interval for the difference between treatments was between 1% and 20%). An ovulation rate of 52% with CC 50 mg/d (the approved starting dose) was assumed on the basis of prior studies (15–17), and the ovulation rate with anastrozole needed to be 50% with a sample size of 41 patients per treatment arm to meet this criterion. Although the cited studies reported ovulation rates of 49.0% (15), 56.6% (16), and 85.3% (17) with CC, it is important to note that all three studies also used CC doses >50 mg. Because the present study was a phase II registration study, the approved starting dose of the reference medication, CC 50 mg administered for 5 days, was mandated (18). Accordingly, the statistical plan incorporated the published ovulation rates for CC 50 mg of 52.1% (190 of 428) and 57.2% (56 of 138) (16, 17); Legro et al. (15) did not report ovulation rates for specific doses of CC.

Secondary endpoints included occurrence of, and time to, LH surge, number of follicles >11 mm in diameter, and endometrial thickness. E_2 levels were also assessed in both ovulatory and nonovulatory patients. Pharmacokinetic and pharmacodynamic profiles of anastrozole were evaluated in cycle 1 in a subgroup of 40 patients.

Safety was assessed by monitoring adverse events (AEs), incidence of cysts >25 mm in diameter, OHSS and OHSS-related symptoms, and clinically significant changes in routine laboratory parameters/vital signs.

All statistical analyses were performed using SAS 6.12 software (SAS Institute, Cary, NC). The primary endpoint was analyzed with the Cochran-Mantel-Haenszel test. All other endpoints were analyzed descriptively.

RESULTS

Patient Disposition

The study was performed between February 2003 and May 2004. In total, 194 patients entered the study and were randomized to one of the five treatment arms. Of these, 133 patients completed cycle 1 without becoming pregnant and underwent a second cycle; 69 patients completed cycle 2 and underwent a third cycle. Overall, 97 of 194 patients (50.0%) completed the study; 37 of 194 patients (19.1%) became pregnant. The most frequently cited single reason for premature withdrawal from the study was lack of efficacy (30 of 194; 15.5%).

Baseline Demographic and Disease Characteristics

Treatment groups were well matched in terms of baseline demographic characteristics, gynecologic history, and uterine features (Table 1). Mean BMI, however, was slightly higher for those patients who did not ovulate compared with those who did. There were no clinically significant differences among the treatment groups at menstrual cycle day 2–3 in prestudy FSH, E_2, DHEA-S, P, total T, TSH, PRL, or androstenedione levels.

Efficacy Data

Cycle 1 Ovulation rates for patients who received anastrozole were 46.2% (5 mg), 41.0% (10 mg), 23.1% (20 mg), and 28.9% (30 mg). The ovulation rate in the CC group was 61.5%. Because the lower bound of the 90% confidence interval for difference in ovulation rates was outside the predefined 20% limit, noninferiority was not demonstrated for any anastrozole dose compared with the CC 50 mg/d dose (Table 2 and Supplemental Result).

Despite lower ovulation rates in the anastrozole groups compared with the CC 50 mg/d group, overall clinical pregnancy rates in cycle 1 were no different for those patients treated with anastrozole 5 mg (12.8%), anastrozole 10 mg (12.8%), and CC 50 mg/d (15.4%) (Table 2 and Supplemental Result).

There was no difference in the percentage of patients treated with anastrozole 5 mg (59.0%) or CC 50 mg/d (61.5%) who experienced a spontaneous midcycle LH surge, whereas the percentage of patients with a spontaneous midcycle LH surge was lower among those receiving anastrozole 10 mg (41.0%), 20 mg (30.8%), or 30 mg (39.5%). The mean (SD) time to spontaneous LH surge was also not different in patients receiving anastrozole 5 mg or CC 50 mg/d (14.7 [3.5] days vs. 15.1 [3.4] days, respectively) but was longer for those receiving higher doses of anastrozole.

Mean (SD) E_2 levels were lower on menstrual cycle day 5–6 in patients receiving anastrozole (overall, 44.7 [21.4] pg/mL) than in those receiving CC 50 mg/d (77.5 [46.5] pg/mL). For patients receiving anastrozole 5 mg in cycle 1, the mean (SD) serum E_2 level