Anastrozole vs. clomiphene citrate in infertile women with ovulatory dysfunction: a phase II, randomized, dose-finding study

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Objective: To determine an effective multiple-dose regimen of anastrozole compared with clomiphene citrate (CC) to induce follicular growth and ovulation in infertile women with ovulatory dysfunction.
Design: Phase II, prospective, randomized, double-blind, multicenter, dose-finding, noninferiority study.
Setting: Outpatient.
Patient(s): Infertile women (n = 271) with ovulatory dysfunction, aged 18–40 years, with body mass index <37 kg/m^2.
Intervention(s): Five days of anastrozole at 1, 5, or 10 mg/d or CC at 50 mg/d.
Main Outcome Measure(s): The primary endpoint was the ovulation rate (mid–luteal phase serum P level ≥ 10 ng/mL or clinical pregnancy) in the first treatment cycle (cycle 1).
Result(s): In cycle 1 the ovulation rates for anastrozole at 1, 5, and 10 mg/d were 30.4% (n = 24), 36.8% (n = 28), and 35.9% (n = 14), respectively, compared with 64.9% (n = 50) for CC at 50 mg/d. In up to three cycles of treatment, cumulative ovulation rates did not differ between groups. No cases of ovarian hyperstimulation syndrome were reported, and both anastrozole and CC were well tolerated.
Conclusion(s): In terms of ovulation rates, 5-day anastrozole at 1, 5, and 10 mg/d was less effective than CC at 50 mg/d for cycle 1 (noninferiority was not shown). (Fertil Steril® 2011;95:1720–4. ©2011 by American Society for Reproductive Medicine.)

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

For the past four decades clomiphene citrate (CC) has been the primary treatment for infertility in World Health Organization group II anovulatory patients. Although ovulation is restored in approximately 70% of treated women, fewer than half achieve pregnancy (see ref. 1 for review). Between 20% and 25% of women do not ovulate with CC (2). Investigators have reported a slight increase in miscarriage rate, perhaps attributed to the fact that 32% of nonovulatory women had endometrial thickness <6 mm on the day after administration of hCG, which may reduce the chance of implantation and successful pregnancy (2). Because CC has a long half-life, it may accumulate in the body, and may lead to long-lasting depletion of estrogen receptors (3), aromatase inhibitors have been proposed as a replacement for CC (2, 4–8).

Anastrozole is a potent and highly selective nonsteroidal aromatase inhibitor. Reducing circulating E_2 levels by 80%, anastrozole has been shown to produce a beneficial effect in women with breast cancer (9). Anastrozole studies in healthy premenopausal women with ovulatory dysfunction have been conducted. In a phase I trial with single doses (5, 10, 15, and 20 mg) and 5-day multiple doses (10 and 15 mg), anastrozole was well tolerated, and the pharmacokinetic profile indicated a promising ovulatory agent (10) (Supplemental Text, available online).

Although the total pregnancy rate was no different for patients receiving a single dose of 5 or 10 mg of anastrozole vs. treatment with CC, ovulation rates were not similar (11). Simulation models suggested that a 5-day anastrozole regimen would improve the ovulation rate. Consequently, a 5-day regimen of anastrozole was investigated. The objectives of the present study were to determine an effective dose of anastrozole to induce follicular growth and ovulation, and to evaluate the safety and tolerability of anastrozole compared with CC in infertile women with ovulatory dysfunction.

MATERIALS AND METHODS

Study Design

Study 25550 (NCT00213148) was a phase II, prospective, randomized, double-blind, multicenter, dose-finding, noninferiority study of multiple-dose anastrozole vs. CC. Twenty-five US sites participated in the study between March 2005 and December 2007. Institutional review board or independent ethics committee approvals were obtained at each center, and the study was conducted in accordance with the Declaration of Helsinki and principles of good clinical practice. All patients provided written informed consent (Supplemental Text).

Patients

Infertile women with ovulatory dysfunction were recruited, aged 18–40 years, inclusive, with a body mass index <37.0 kg/m^2, two patent fallopian

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tubes, and two functional ovaries. The patient's usual cycle length had to be either <21 or >35 days with six or more menses per year or >35 days with fewer than six menses per year and a positive response to a progestin challenge within the last 6 months.

All screening assessments were to be completed within 6 weeks of treatment (Supplemental Text).

Treatment Schedule

Patients were randomized on day of treatment initiation to one of four groups in a 1:1:1:1 ratio stratified by center and ovulatory dysfunction in cycle 1, according to a central randomization system.

The double-blind design was maintained through the use of prepackaged drug kits, according to the stratified randomization list. A daily oral dose was administered for 5 consecutive days in each group, starting on menstrual cycle day 2 or 3, as follows: anastrozole (Arimidex; AstraZeneca UK, Macclesfield, United Kingdom) at 1, 5, or 10 mg/d, or CC (Serophene; TEVA Pharmaceuticals, Petach Tikva, Israel) at 50 mg/d, in addition to the matching placebo assigned to each group.

Patients returned to the clinic on stimulation day 3 or 4 (defined as the first day of anastrozole or CC administration) and day 6 or 7 for serum E_2 measurement and transvaginal ultrasound scan (TVUS). These measurements were repeated until an LH surge occurred. Within 24 hours of the LH surge, patients had sexual intercourse or IUI. On days 6/7 and 8/9 after the LH surge, patients returned for a TVUS and P measurement. If an LH surge was not detected, patients returned for a P sample 1 week after their last TVUS date for that cycle (Supplemental Text).

Ovulation was confirmed by a P level ≥10 ng/mL. In ovulatory cycles, a pregnancy test was performed between days 15 and 20 after LH surge. Patients with positive pregnancy test results (serum hCG level >10 mIU/mL) had the test repeated within 2–4 days and returned to the clinic 35–42 days after LH surge for a confirmatory TVUS.

Two additional treatment cycles were permitted if patients failed to achieve clinical pregnancy in their first treatment cycle. Doses used in subsequent cycles were determined by a dose-adjustment algorithm based on the previous cycle response (Supplemental Text). In the subsequent cycle, treatment was initiated on cycle day 2 or 3.

Criteria for treatment discontinuation included excessive response (four or more follicles >17 mm in diameter, with or without ovulation, wherein IUI or intercourse was disallowed), ovarian hyperstimulation syndrome (OHSS), occurrence of toxicity grade 2+ according to Common Toxicity Criteria, or persistence of an ovarian cyst >25 mm in diameter that did not resolve after one rest cycle without therapy for 1 month.

Assessments and Analyses

The primary endpoint was cycle 1 ovulation rate (midluteal serum P level ≥10 ng/mL and/or pregnancy [hCG level >10 mIU/mL]). Because this was a noninferiority study, a noninferior anastrozole dose was determined if the 97.5% one-sided lower confidence bound of the difference in ovulation rates (anastrozole minus CC) was at least −20%. Ovulation rates were assumed to be approximately 62% for the CC group. To provide 70% power at a one-sided significance level of 2.5%, a total of 224–292 evaluable patients were required.

The interim analysis and adaptive design relating to the primary endpoint and the major secondary endpoint are described in detail in the Supplemental Text.

The major secondary endpoint was clinical pregnancy, defined as the presence of an intrauterine gestational sac with cardiac activity, confirmed by TVUS.

Other secondary endpoints are provided in Results. Primary safety assessments included incidence of multiple pregnancy, adverse events (AEs), and OHSS. A subgroup of patients was selected for additional pharmacokinetic and pharmacodynamic analysis in cycle 1 only (Supplemental Text).

Statistical analyses were performed using SAS 8.2 (SAS Institute, Cary, NC). All patients who received at least one dose of anastrozole or CC were included in the all-treated population. Hochberg's multiple comparison procedure was used in the analysis of all efficacy parameters. Only the primary and major secondary endpoints were analyzed using inferential statistics (χ^2 analysis and Fisher's exact test). All other endpoints were analyzed descriptively.

RESULTS

Patient Disposition

In total, 271 patients were randomized and received at least one dose of study drug. In cycle 1, 221 patients (81.5%) completed the cycle. For the 50 patients who did not complete cycle 1, the most common reason was lack of efficacy (n = 25); other reasons were loss to follow-up (n = 6), protocol violation (n = 2), an AE (n = 1), a pregnancy unrelated to therapy (n = 1), a nonresolving ovarian cyst >25 mm in diameter (n = 1), and "other" reasons (n = 14). Twenty-seven patients became pregnant in cycle 1, and 188 patients went on to cycle 2; 128 completed cycle 2, with 21 achieving pregnancy. Of the 105 patients who went on to cycle 3, 100 completed treatment and 5 achieved pregnancy. Overall, the most frequently cited reason for treatment failure was failure of ovulation. Discontinuation due to lack of efficacy was similar across the treatment groups.

Demographic, historic gynecologic, and obstetric characteristics were similar across all treatment groups (Table 1 and Supplemental Text).

Efficacy Data

Cycle 1 The ovulation rate for anastrozole-treated patients was 30.4% (1 mg), 36.8% (5 mg), and 35.9% (10 mg), compared with

TABLE 1

Baseline demographics and clinical characteristics.

Characteristic	Anastrozole 1 mg (n = 79)	Anastrozole 5 mg (n = 76)	Anastrozole 10 mg (n = 39)	CC 50 mg (n = 77)
Age (y)	28.8 (3.9)	29.6 (3.9)	29.3 (3.4)	29.2 (3.8)
BMI (kg/m^2)	28.6 (5.1)	27.2 (5.5)	27.9 (5.8)	28.1 (5.4)
Primary infertility, n (%)	60 (75.9)	53 (69.7)	30 (76.9)	48 (62.3)
Duration of infertility (mo)	43.2 (37.1)	36.4 (29.8)	39.5 (28.2)	34.0 (29.1)
Last menses induced, n (%)	43 (54.4)	32 (42.1)	22 (56.4)	32 (41.6)
PCOS[a], n (%)	65 (82.3)	61 (81.3)	34 (87.2)	62 (81.6)
Prior CC usage, n (%, range of no. of cycles)	51 (64.6, 1–6)	52 (68.4, 1–6)	21 (53.8, 1–6)	45 (58.4, 1–6)

Note: Values are expressed as mean (SD) unless indicated otherwise. BMI = body mass index; CC = clomiphene citrate; PCOS = polycystic ovarian syndrome.

[a] PCOS was defined as oligoanovulation (90.1%), hyperandrogenism (32.4%), and/or polycystic ovaries (64.9%).

Tredway. Five-day anastrozole in infertility. Fertil Steril 2011.