Letrozole vs. clomiphene citrate in patients with ovulatory infertility

Ülkü Bayar, M.D., H. Alper Tanrıverdi, M.D., Aykut Barut, M.D., Ferruh Ayoğlu, M.D., Oya Özcan, M.D., and Erdal Kaya, M.D.

Departments of Obstetrics and Gynecology and Public Health, University of Karaelmas, Zonguldak; and Doctor Zekai Tahir Burak Maternity Hospital, Ankara, Turkey

Objective: To compare the effectiveness of letrozole and clomiphene citrate (CC) in ovulatory patients with borderline male factor infertility, early stage endometriosis, and unexplained infertility.

Design: Prospective quasi-randomized trial.

Setting: University infertility clinic.

Patient(s): Forty-six consecutive patients with ovulatory infertility were recruited. Twenty-five patients (67 cycles) were given CC and 21 patients (52 cycles) were given letrozole. Both drugs were given orally on days 3–7 of menses.

Intervention(s): Letrozole, CC, ovulation induction, IUI, timed intercourse.

Main Outcome Measure(s): Number of follicles, endometrial thickness, and pregnancy rates.

Result(s): The median serum E2 concentration on the day of hCG administration in the letrozole and CC groups were 191.5 pmol/L and 476.0 pmol/L, respectively. The median endometrial thickness on the day of hCG were 8 mm in both groups. Ovulation occurred in 81% (42/52) of the letrozole-treated and 85% (57/67) of the CC-treated patients. Pregnancy rate (PR) per cycle was 9% (5/52) in the letrozole group and 12% (8/67) in the CC group.

Conclusion(s): Letrozole and CC have comparable effectiveness in ovulatory patients with borderline male factor infertility, early stage endometriosis, and unexplained infertility. (Fertil Steril 2006;85:1045–8. ©2006 by American Society for Reproductive Medicine.)

Key Words: Letrozole, clomiphene citrate, ovulation induction, ovulatory infertility
Basle, Switzerland) and CC (Gonaphane, Organon, Santa Farma İlaç Sanayi, Sirkeci, Istanbul, Turkey) were given orally in doses of 2.5 mg/day and 100 mg/day, respectively, from menstruation days 3–7. Patients were monitored with transvaginal ultrasonography and serial measurements of E2 starting on day 7 of the cycle. Human chorionic gonadotropin (Pregnyl, Organon, Santa Farma İlaç Sanayi, Sirkeci, İstanbul, Turkey) at a dose of 10,000 IU was used to trigger ovulation when at least one follicle exceeding 18 mm in diameter was noted.

Intrauterine insemination was performed in patients with borderline male factor infertility both in the letrozole (n:27) and CC (n:36) groups. Timed intercourse was recommended in the remaining patients in both groups. Double IUI was performed 24 and 48 hours after administration of hCG. Ovulation was assumed to have occurred when midluteal serum P exceeded 5 ng/mL.

Intra-assay and interassay coefficients of variations of FSH, E2, and P were as follows: FSH (analytical sensitivity: 0.1 mIU/mL, intra-assay coefficient of variation [CV]: 1.90%, interassay CV: 2.11%), E2 (analytical sensitivity: 15 pg/mL, intra-assay CV: 2.50%, interassay CV: 3.23%), and P (analytical sensitivity: 0.1 ng/mL, intra-assay CV: 1.13%, interassay CV: 1.72%).

The statistical analyses were performed using SPSS for Windows (SPSS Inc., Zonguldak Karaelmas University, Zonguldak, Turkey) statistical package. The data were expressed as median (range). Mann-Whitney U and Kruskal-Wallis tests were used to compare nonparametric data. The correlation between endometrial thickness and E2 was studied with Pearson correlation test. Type 1 error was set at 0.05. A sample size of at least 45 cycles in each group was required to detect a difference of 250 pmol/L in E2 and a difference of two follicles on day of hCG administration between the two groups. This sample size is also sufficient to detect an odds ratio (OR) of 4 between these groups, with a α (type I error) set at 0.05, and 80% power.

RESULTS

One hundred nineteen cycles of ovulation induction were carried out in 46 patients. The median age, day 3 FSH, and E2 levels were comparable among the letrozole and CC groups (Table 1). The median duration of infertility was significantly higher in the letrozole group (P=.01) (Table 1). In the letrozole group, infertility was due to male factor in 12 cases (57%), minimal–mild endometriosis in 3 cases (14%), and unexplained in the remaining 6 cases (29%). In the CC group, the respective figures were comparable and were 14 (56%), 3 (12%), and 8 (32%).

Four patients in the letrozole group were lost to follow-up. The remaining 21 patients in the letrozole group underwent 52 ovulation induction cycles. Patients were scheduled for timed intercourse in 25 cycles and IUI in 27 cycles. Twenty-five patients in the CC group underwent 67 ovulation induction cycles. Patients were scheduled for timed intercourse in 31 cycles and IUI in 36.

The ovulation induction data of the two groups are given in Table 2. The median number of follicles >15 mm in diameter was comparable between the two groups, with a median of 1 (0–4) in the letrozole group and 1 (0–5) in the CC group (P=.61). The median endometrial thickness on the day of hCG was 8 (5–12) mm in the letrozole group and 6 (3–11) mm in the CC group (P=.11). The median E2 level on the day of hCG was 191.5 (46–1204) pg/mL in the letrozole group and 476.0 (48–2326) pg/mL in the CC group (P=.001). The median E2 per follicle >15 mm in diameter on the day of hCG was 170.5 (46–949) pg/mL in the letrozole group and 358.0 (48–1313) pg/mL in the CC group (P=.003). The pregnancy rate per cycle was 5/52 (10%) in the letrozole group and 8/67 (12%) in the CC group (P=.9).

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic features and ovarian reserve of the letrozole and CC-treated groups.</td>
</tr>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>No. of cycles performed</td>
</tr>
<tr>
<td>Female age (y)</td>
</tr>
<tr>
<td>Duration of infertility</td>
</tr>
<tr>
<td>Day-3 FSH (mIU/mL)</td>
</tr>
<tr>
<td>Day-3 E2 (pg/mL)</td>
</tr>
</tbody>
</table>

*Note: Values are median (range).*

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation induction outcome of the letrozole and CC groups.</td>
</tr>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>No. of follicles &gt;15 mm in diameter on the day of hCG</td>
</tr>
<tr>
<td>Endometrial thickness the day of hCG (mm)</td>
</tr>
<tr>
<td>E2 level on the day of hCG (pg/mL)</td>
</tr>
<tr>
<td>E2 per follicle &gt;15 mm in diameter on the day of hCG (pg/mL)</td>
</tr>
<tr>
<td>Pregnancy rate per cycle (%)</td>
</tr>
</tbody>
</table>

*Note: Pregnancy rate per cycle is expressed as N (%), all other values are median (range).*

diameter and endometrial thickness on the day of hCG administration were comparable among the two groups. In the CC group, the bilayer endometrial thicknesses on the day of hCG administration was >5 mm in 61 cycles; in the remaining 6 (9%) cycles it was <5 mm. None of these six cycles resulted in pregnancy. The bilayer endometrial thickness was >5 mm in all cycles in the letrozole group. Although there was a significant positive correlation between endometrial thickness and E2 in the letrozole group (r = 0.62 and P<.01), no such significant correlation was noted in the CC group (r = 0.20 and P>.05).

The median E2 level on the day of hCG administration was significantly lower in the letrozole group (P=.001) (Table 2). The median E2 level per follicle >15 mm in diameter was significantly lower in the letrozole group (P=.003) (Table 2). Ovulation occurred in 81% (42/52) and 85% (57/67) of the cycles in letrozole and CC groups, respectively (P=.71). Five (9%) and eight (12%) patients conceived in the letrozole and CC groups, respectively (P=.9) (Table 2). Two (7.4%) and three (8.3%) patients conceived with IUI cotreatment in the letrozole and CC groups, respectively. Other than a single case of miscarriage in the CC group, the remaining 12 pregnancies resulted in healthy term delivery. No multifetal pregnancy or side effects were noted in the letrozole and the CC groups.

DISCUSSION

Letrozole (4, 4’-[1H-1, 2, 4-triazol-1-ylmethylene]-bis-benzonitrile) is a type II, third generation, cytochrome P-450 linked aromatase inhibitor that reversibly suppresses E biosynthesis. When administered in the early follicular phase, letrozole, by blocking E synthesis reduces the negative feedback effect of E on the hypothalamus or hypophysis. This results in an increased secretion of gonadotropins similar to the effect of CC. When used in the follicular phase of the cycling Bonnet monkeys, letrozole has been noted to increase serum gonadotropin, A levels, and stimulate follicular maturation (8). Letrozole was shown to increase LH and T levels in rats (9). In primates a stimulatory effect of androgens on follicular growth by amplification of FSH gene expression has been reported (10, 11). Letrozole may induce accumulation of ovarian A and thus increased expression of FSH receptors resulting in increased sensitivity of the developing follicles to FSH (10, 11). High oral bioavailability and relatively short half-life (45 hours) make letrozole a suitable agent for ovulation induction (12).

There is a paucity of data on the use of letrozole as an ovulation induction agent in anovulatory infertility (4) and as a part of empirical treatment (5, 13–15). Mitwally and Casper (4) have reported the use of letrozole in 12 patients with polycystic ovary syndrome (PCOS) and 10 patients with ovulatory infertility. Letrozole was given in a dose of 2.5 mg on days 3–7 of menses. In the PCOS group, ovulation occurred in nine patients (75%) and pregnancy was achieved in three (25%). In ovulatory patients, ovulation occurred in all cycles. The mean number of follicles measuring >15 mm in diameter on the day of hCG administration was 2.3 (range, 1–4). One pregnancy (10%) was reported.

Mitwally and Casper (16), in another study, evaluated the use of letrozole with exogenous FSH in 12 patients with unexplained infertility and a history of poor ovarian response to FSH in at least two previous cycles. Previous poor response was defined as less than three follicles 18 mm in diameter on the day of hCG administration (17). Letrozole was administered from days 3–7 at a dose of 2.5 mg/day and FSH treatment (50–225 IU/day) was started on days 5–7. Intrauterine insemination was performed in all cycles. Improved response to exogenous FSH stimulation with letrozole cotreatment was noted by the significantly lower FSH dose associated with significantly higher number of mature follicles. Three (21%) pregnancies were achieved. Healey et al. reported similar findings in 205 IUI cycles; addition of letrozole to FSH treatment decreased FSH requirement and increased the number of preovulatory follicles (13). Although endometrial thickness was decreased, no negative effect on pregnancy rates (PR) was noted.

In this study we compared letrozole with CC as the first-line therapy for ovulation induction in patients with borderline male factor infertility, early-stage endometriosis, and unexplained infertility. Being not a blinded study and quasi-randomization are weaknesses of our study. Because our study was a pilot study and the sample size limited, the duration of infertility was significantly higher in the letrozole group. Despite this significant difference PRs of two groups were comparable. All ovulation induction outcome measures, excluding serum E2 level and E2 level per follicle >15 mm in diameter, were comparable among the CC and letrozole groups. Pregnancy rates were also comparable.

Although median endometrial thickness was comparable among the CC and letrozole groups, it was less than 5 mm in six CC cycles; however, in none of the letrozole cycles it was less than 5 mm. Although, our sample size is limited, a lack of detrimental effect on endometrial thickness may be a favorable finding with letrozole treatment. There are limited data on the effect of letrozole on endometrium. Cortinez et al. (14), in letrozole-treated patients, reported normal morphology of endometrium and full expression of pinopodes during the implantation window. Mitwally and Casper (4) reported significantly higher endometrial thickness on the day of the hCG administration with letrozole compared with CC, despite significantly lower E2 levels in the former. On the other hand, no significant difference was noted in other studies (14, 17), including an animal study (18).

Due to significantly lower E2 levels, letrozole may be considered for empirical ovulation induction in infertile patients with E-dependant neoplasms. We conclude that letrozole is as effective as CC and may be an alternative to CC in ovulation induction protocols for both IUI and timed intercourse.
Acknowledgments: The authors are grateful to Professor Vildan Sümbülog˘lu for her valuable contribution in statistical analyses of the data.

REFERENCES