Original Article

Letrozole and desogestrel-only contraceptive pill for the treatment of stage IV endometriosis

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Abstract

Background: It has recently been suggested that aromatase inhibitors may effectively reduce pain symptoms related to the presence of endometriosis both in postmenopausal women and in subjects of reproductive age.

Aims: This study aims to evaluate the effectiveness of a combination of letrozole and desogestrel in the treatment of pain symptoms related to the presence of endometriosis.

Methods: This open-label prospective study included 12 women with endometriosis-related pain symptoms that were refractory to previous medical and surgical treatments. All women had previous laparoscopy documenting stage IV endometriosis. The treatment protocol included the daily oral administration of letrozole 2.5 mg (Femara®), desogestrel 75 μg (Cerazette®), elemental calcium 1000 mg and vitamin D 880 I.U. The scheduled treatment period was six months.

Results: None of the women included in the study completed the six-month treatment because all patients developed ovarian cysts; the median length of treatment was 84 days (range, 56–112). At interruption of treatment, all women reported significant improvements in dysmenorrhoea and dyspareunia. Pain symptoms quickly recurred at three-month follow up. There were no severe adverse effects of treatment; no significant change in the mineral bone density was observed during treatment.

Conclusions: The combination of letrozole and desogestrel induces a relief of pain symptoms in women with endometriosis but it causes the development of ovarian cysts. Pain symptoms quickly recur after the completion of treatment.

Key words: aromatase inhibitors, chronic pelvic pain, deep dyspareunia, dysmenorrhoea, endometriosis, letrozole.

Introduction

In the last few years, our understanding of the pathogenesis of endometriosis at the cellular and molecular levels has significantly improved; based on these findings, new agents have been proposed for the medical treatment of endometriosis.[1] Noble *et al.*[2] demonstrated that cytochrome P-450 aromatase contributes to the pathogenesis of endometriosis having aberrant expression on both eutopic and ectopic endometrium of subjects affected by the disease. This enzyme is responsible for catalysing the conversion of androstenedione and testosterone to estrone and estradiol. Owing to the hormone-dependent character of endometriosis, the presence of aromatase and the consequent local oestrogen production may promote the growth of endometriotic implants.

On the basis of these molecular observations, case reports and pilot studies suggested that aromatase inhibitors may effectively reduce pain symptoms related to the presence of endometriosis both in postmenopausal women[3,4] and in subjects of reproductive age.[5–8] Aromatase inhibitors are now an integral part of postmenopausal breast cancer therapy; but information regarding their use in women of reproductive age is still limited. By blocking the conversion of androgens to oestrogens in ovarian granulosa cells, these drugs reduce the negative feedback at the pituitary–hypothalamus level, and therefore increase serum follicle-stimulating hormone levels that stimulate the development of ovarian follicles.[9]

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Thus, when aromatase inhibitors are administered to premenopausal women for the treatment of endometriosis, they must be combined with a gonadotropin-blocking agent (such as progesterone, progestins or oral contraceptive pill) in order to prevent the development of functional ovarian cysts.[5–7]

This study evaluates the effectiveness of a combination of letrozole and desogestrel-only contraceptive pill in the treatment of pain symptoms related to the presence of endometriosis.

Methods

Study population

This open-label prospective study enrolled 12 women with endometriosis-related pain symptoms (dysmenorrhoea, deep dyspareunia, and/or chronic pelvic pain) that were refractory to previous medical and surgical treatments. Inclusion criteria for the study were as follows: women of reproductive age with regular menstrual cycles; previous laparoscopy documenting stage IV endometriosis according to the revised American Fertility Society classification;[10] dysmenorrhoea and/or chronic pelvic pain that persisted or recurred after one or more previous treatments employing surgery and/or GnRH analogs. Before enrolment in the study, patients underwent transvaginal ultrasound and magnetic resonance imaging. Multi-slice computerised tomography after colon distension with a water enema was performed to rule out bowel endometriosis;[11] in some cases, pyelography was performed to exclude ureteral obstruction. All prior hormonal therapies had to be completed at least three months before study entry. Pain symptoms were experienced for at least one year before study entry. Women with ovarian endometriomas and/or bowel endometriotic nodules were excluded from the study. Other study exclusion criteria were ovarian cysts ≥ 2 cm; undiagnosed vaginal bleeding; osteopenia or osteoporosis; smoking; current or past history of seizure disorders; pulmonary, cardiac, hepatic, or renal disease; thromboembolic or cerebrovascular events; pregnancy; and desire to conceive within one year after the completion of the treatment.

Study protocol

The treatment protocol included the daily oral administration of letrozole 2.5 mg (Femara®, Novartis Farma, Varese, Italy), desogestrel 75 μg (Cerazette®, Organon, Rome, Italy), elemental calcium 1000 mg and vitamin D 880 I.U. (Calcit Vitamina D3®, Procter & Gamble, Rome, Italy). The scheduled treatment period was six months. Medications were started on the second day of the menstrual cycle.

Evaluation of patients

Pain symptoms were evaluated before starting the treatment, monthly during the treatment, at three and six months from the interruption of treatment. A standardised questionnaire was used to evaluate the presence of dysmenorrhoea, deep dyspareunia, and chronic pelvic pain; the intensity of each pain symptom was measured on a 100-mm visual analog scale (VAS), the left extreme indicating the absence of pain, and the right indicating pain as bad as it could be. Women kept a diary for recording the side-effects of treatment. Patients were followed on a monthly basis during treatment; at each visit a transvaginal ultrasound was performed and side-effects of treatment were reviewed. Complete blood count, serum electrolytes, lipids, and kidney and liver function tests were measured before the onset of therapy, monthly during treatment, and at the completion of treatment. A bone densitometry determination of the hip and lumbar spine (by dual-energy X-ray absorptiometry or DEXA scan) was performed within one month before the onset of the study and was repeated within one month after completion of the treatment. During the six months follow up, the patients were advised to use non-hormonal contraception devices to prevent pregnancy. The study protocol was approved by the local Institutional Review Board of San Martino Hospital, Genoa, Italy. A written informed consent was signed by the patients enrolled in the study.

Statistical analysis

Data distribution was determined using the Shapiro–Wilks test. Comparisons were conducted using Student's *t*-test and Mann–Whitney *U*-test. Calculations were performed using the SPSS software package (release 10.0.5, SPSS Inc., Chicago, IL, USA). A *P*-value less than 0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

The mean ($\pm$ SD) age of the study population was 32.8 ± 3.2 years; two women had previous pregnancies. Ten women (83.3%) were previously treated with sequential oral contraceptive pill, four women (33.3%) received continuous oral contraceptive pill, eight patients (66.7%) used GnRH analogs and one woman (8.3%) received danazol. Before treatment, all patients suffered dysmenorrhoea; 66.7% of sexually active women (six of nine) had deep dyspareunia; and 58.3% of the subjects had chronic pelvic pain.

Pain symptoms during treatment and at follow up

None of the women included in the study completed the six-month treatment, because all the patients developed functional ovarian cysts. The treatment was interrupted after two months in two patients, after three months in seven patients, and after four months in the remaining three patients. The median length of treatment was 84 days (range, 56–112). The mean ($\pm$ SD) largest diameter of the functional ovarian cysts was 5.0 ± 1.3 cm (range, 3.5–8.0 cm); eight women (66.7%) developed more than one ovarian cyst. At the interruption of treatment, all women reported a significant

Table 1 Pain symptoms evaluated at the interruption of the treatment

	Baseline (*n*)	Interruption of treatment (*n*)	*P*-value
Presence of the symptom†			
Dysmenorrhoea	12/12 (100%)	0/12 (0.0%)‡	< 0.001
Deep dyspareunia	6/9 (66.7%)	0/9 (0.0%)	0.005
Chronic pelvic pain	7/12 (58.3%)	4/12 (33.3%)	0.207
Intensity of the symptom§			
Dysmenorrhoea	8.7 ± 1.9	0.8 ± 0.7‡	*P* = 0.028
Deep dyspareunia	6.5 ± 2.7	0.6 ± 0.5	*P* = 0.002
Chronic pelvic pain	6.0 ± 1.9	3.2 ± 2.6	*P* = 0.097

†Patients were considered to have the symptom when its intensity on the visual analog scale was > 3.
‡Measured at the first menstrual period following interruption of treatment.
§Data are presented as mean ± SD.

Table 2 Pain symptoms at three and six months follow up

	Baseline (*n*)	3 months follow up	6 months follow up
Presence of the symptom†			
Dysmenorrhoea	12/12 (100%)	11/12 (91.7%)	12/12 (100.0%)
Deep dyspareunia	6/9 (66.7%)	6/9 (66.7%)	6/9 (66.7%)
Chronic pelvic pain	7/12 (58.3%)	7/12 (58.3%)	7/12 (58.3%)
Intensity of the symptom‡			
Dysmenorrhoea	8.7 ± 1.9	6.8 ± 1.7§	8.8 ± 1.4
Deep dyspareunia	6.5 ± 2.7	5.6 ± 2.2	6.4 ± 1.9
Chronic pelvic pain	6.0 ± 1.9	5.9 ± 2.0	6.0 ± 1.5

†Patients were considered to have the symptom when its intensity on the visual analog scale was > 3.
‡Data are presented as mean ± SD.
§*P* = 0.008 when compared with baseline values.

improvement in dyspareunia; improvements were observed in the presence and intensity of chronic pelvic pain, but they did not reach statistical significance when compared with baseline values. The intensity of dysmenorrhoea was significantly reduced at the first menstrual cycle following the interruption of treatment when compared with baseline values (Table 1). Pain symptoms quickly recurred at three-month follow up. At six-month follow up, the intensity of dysmenorrhoea and dyspareunia was similar to baseline values (Table 2).

Side-effects of treatment

There were no adverse effects on blood count, liver function, renal function, and lipid profile (data not shown). DEXA scans were performed in all patients before the enrolment; a second DEXA was performed only in the women treated for at least three months ($n = 10$). No significant change in the mineral bone density was observed during treatment both in the lumbar spine ($P = 0.912$) and in the hip ($P = 0.631$). The following side-effects were reported by the patients: vaginal bleeding ($n = 9$, 75.0%), weight gain ($n = 6$, 50.0%), abdominal bloating ($n = 5$, 41.7%), depression ($n = 4$, 33.3%), asthenia ($n = 4$, 33.3%), musculoskeletal pain ($n = 2$, 16.7%), nausea ($n = 2$, 16.7%), headache ($n = 2$, 16.7%), and peripheral oedema ($n = 1$, 8.3%).

Conclusion

In the present study, we observed that the combination of letrozole and desogestrel may temporarily reduce the intensity of dysmenorrhoea and deep dyspareunia in women with stage IV endometriosis; there was a reduction in the intensity of chronic pelvic pain but it did not reach statistical significance. Unfortunately, this double-drug regimen caused the formation of ovarian cysts in all the patients and the majority of women developed more than one cyst. These findings are in line with a limited number of pilot studies that previously demonstrated an improvement in pain symptoms related to the presence of endometriosis during treatment with aromatase inhibitors.[6–8] Surprisingly, none of these studies reported a follow up after the completion of the treatment with aromatase inhibitors. The current study demonstrates for the first time that pain symptoms quickly recur after interrupting the treatment with aromatase inhibitors; in particular, in all women, the characteristics of pain symptoms at six-month follow up were identical to baseline values. These findings are in contrast with a case report by Shippen and West.[5] Anastrozole, together with oral progesterone, was given to two premenopausal sisters with endometriosis; the medications were administered for six months (21 days of therapy, followed by seven days off); additionally, rofecoxib 12.5 mg was administered once a day continuously for the

28-day cycle. This therapy resulted in a rapid and progressive reduction in symptoms over three months, with the maintenance of remission of symptoms for more than 24 months after treatment in both cases. The reasons of these different observations remain unclear. We are aware that a limitation of our study consists in the fact that the patients received the treatment protocol for a limited period of time (median 84 days); a longer period of treatment may reduce the risk of pain recurrence after the completion of therapy.

Another limitation of this study consists in the fact that it was not a randomised placebo-controlled trial; therefore, the knowledge of the treatment received may have theoretically biased the pain scores reported by the patients. In addition, a double-drug regimen (letrozole and desogestrel) was administered to the patients and, therefore, we cannot determine the effect of each drug on the improvement of pain symptoms. However, it is well known that aromatase inhibitors cannot be administered alone to premenopausal women due to their ability to stimulate the ovary and induce cyst formation.[9] In the current trial, we chose to combine letrozole with desogestrel; unfortunately, this double-drug regimen did not prevent the development of functional ovarian cysts. Desogestrel was chosen because it has been proven to effectively inhibit ovulation.[12] In addition, it has a good progestin selectivity that determines favourable effects on lipoprotein metabolism and absence of adverse systemic effects (particularly on blood pressure and bodyweight).[13] A final possible criticism to the present study consists in the fact that women included in the study had pain symptoms that were refractory to previous medical and surgical treatments of endometriosis. This population was suitable for investigating the effect of aromatase inhibitors that are not an established treatment for endometriosis, but obviously the findings of this study cannot be extended to the all women with endometriosis.

Information regarding the use of aromatase inhibitors in women of reproductive age is still limited and cannot be deduced from the present study. Although we did not observe detrimental effect on mineral bone density or other severe adverse events, the limited number of patients included in the study and the short period of treatment do not allow drawing conclusions on the safety of these drugs during reproductive age.

In conclusion, the present study suggests that the combination of letrozole with the desogestrel-only contraceptive pill may temporarily reduce dysmenorrhoea and deep dyspareunia related to the presence of endometriosis. However, this double-drug regimen causes the formation of ovarian cysts, and pain symptoms quickly recur after interrupting the treatment. Further studies should determine whether a longer administration of aromatase inhibitors may determine a persistent improvement in pain symptoms with minimal and acceptable side-effects.

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