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Aromatase inhibition for refractory endometriosis-related chronic pelvic pain

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Abstract

Objective—To evaluate the use of an aromatase inhibitor for the treatment of endometriosis-related chronic pelvic pain.

Design—Retrospective analysis.

Setting—Academic medical center outpatient reproductive endocrinology clinic.

Patient (s)—Sixteen patients with endometriosis and chronic pelvic pain who previously failed conventional medical and/or surgical therapy.

Intervention (s)—Treatment with the aromatase inhibitor letrozole (2.5 mg/d) plus a gonadotropin suppressor (norethindrone acetate, 2.5 mg/d, or a combination oral contraceptive [OC]) for an average of 6 months.

Main Outcome Measure (s)—Pain scores were reported at each visit using a visual analogue scale from 0 to 10 (0: no pain, 10: maximum pain).

Result (s)—Sixteen patients were treated with an aromatase inhibitor for 180 ± 31 days. The median pain score at the start of therapy was 7, and at the end of therapy it was 1.5. In the nine patients who were evaluated after discontinuing therapy, pain scores returned to pretreatment levels. We did not find any correlation between the length of treatment and the overall improvement in pain score.

Conclusion (s)—Letrozole plus a gonadotropin suppressor substantially improved pain symptoms in patients with endometriosis refractory to conventional therapies; however, pain recurred after treatment was completed.

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Keywords

Endometriosis; pelvic pain; letrozole; aromatase inhibitor

Endometriosis is an estrogen (E)-dependent disease characterized by ectopic endometrium-like tissue located primarily on pelvic peritoneum and ovaries. Endometriosis is the most common cause of chronic pelvic pain, affecting more than 6%–10% of US women of reproductive age or 4–6 million women (1). In the United States, endometriosis is the third most common gynecologic disorder requiring hospitalization, is commonly implicated in dyspareunia and infertility, and is a leading cause for hysterectomy. Only 50% of women with endometriosis achieve pain relief in response to existing hormonal treatments or conservative surgery (2). There is a clear need to develop novel, effective therapies for endometriosis.

The clinical significance of E biosynthesis in endometriosis is exemplified by the clinical observation that E is essential for the growth of endometriosis. We and other investigators (3–9) have demonstrated abundant aromatase expression and local E production in endometriotic tissue, and animal models have demonstrated reduction in the size of peritoneal endometriotic implants in rats and mice treated with the aromatase inhibitor (AI) letrozole (Femara; Novartis) (10–12). These findings prompted us and other investigators to clinically target aromatase in endometriosis using its third generation inhibitors. Among these inhibitors, anastrozole (Arimidex; AstraZeneca) and letrozole were described in case reports and case series in which endometriosis was successfully treated in both postmenopausal and premenopausal women (13–15). These results suggested that AIs might treat endometriosis more effectively than GnRH analogues by suppression of local E formation in endometriotic tissue.

The purpose of this study is to evaluate our experience with the use of AIs in patients with chronic pelvic pain secondary to endometriosis. Patients elected this experimental therapy after failing conventional treatments or refusing conventional therapy because of known side effects.

MATERIALS AND METHODS

We conducted a retrospective chart review of all patients with endometriosis and pelvic pain treated with AIs in the outpatient reproductive endocrinology clinic of the Northwestern Medical Faculty Foundation at Northwestern Memorial Hospital between June 2003 and May 2005. Demographic information and previous medical and surgical histories were extracted from charts. Data regarding the diagnosis of endometriosis, the type and severity of symptoms, and all surgical and medical therapies attempted before the introduction of AIs was collected. Pain scores were reported at each visit using a visual analogue scale from 0 to 10 (0: no pain; 10: maximum pain), and all reported side effects were recorded.

The study was approved by Northwestern University's Institutional Review Board. The lead author is a consultant with Novartis and Merck Sharp and Dohme Corp., but this study was unfunded.

Statistical Analysis

Data were analyzed retrospectively, and sample size was defined by the study interval and number of patients treated with AI. Data were analyzed using Wilcoxon signed rank tests or Spearman correlation coefficients. All tests were two-tailed and statistical significance was indicated when $P < .05$.

RESULTS

The patients referred to our reproductive endocrinology clinic with pelvic pain due to endometriosis had either failed conventional treatment or sought experimental therapy with AIs to avoid known side effects of conventional therapies. Sixteen patients with surgically confirmed endometriosis and chronic pelvic pain were treated with an AI between June 2003 and May 2005. Patients were prescribed a treatment regimen containing letrozole (a third generation AI) at a dose of 2.5 mg/d as well as suppressive therapy with either a progestin or oral contraceptive (OC) pills. One patient was initially started on anastrozole (1 mg/d), but after 2 months was switched to letrozole. Fourteen patients were prescribed norethindrone acetate at a dose of 2.5 mg daily as suppressive therapy, and two patients were continued on their previously prescribed combination OC pills. Therapy was recommended for 6 months. Patients were evaluated at varying intervals through office visits and telephone encounters.

Although 25 patients were initially offered AI treatment, 7 patients were lost to follow-up after their initial visit, and therefore their response to AI is unknown. Two patients chose not to take the medication, one patient due to cost and the other due to personal preference.

The group's median age was 28 years old. Thirteen patients (81%) were nulliparous and 14 patients (87.5%) were premenopausal (Table 1). Three patients had previously undergone hysterectomy with bilateral oophorectomy for pelvic pain, and one patient was subsequently diagnosed with ovarian remnant syndrome after presenting with persistent pelvic pain, ovarian cysts, and a premenopausal FSH level.

Before presenting to the reproductive endocrinology clinic at Northwestern Memorial Hospital, all 16 patients had taken OC pills, 10 patients had previously used GnRH agonists, and 5 had used medroxyprogesterone acetate (MPA) (Table 2). All patients had undergone at least one laparoscopic procedure for diagnostic or therapeutic purposes. The median number of laparoscopic procedures per patient was two, ranging between one and five procedures per patient. All patients in this study had already failed at least two types of therapy.

Five patients had a documented staging of their disease based on the American Society for Reproductive Medicine revised classification of endometriosis (16). Two patients had a diagnosis of stage 4 endometriosis, and these patients were among the nine patients who completed the recommended 6 months of therapy. One patient had stage 3 endometriosis and two patients had stage 2 endometriosis. The stage of the remaining patients was unknown.

Seven patients discontinued therapy before completing the recommended 6-month course. Of these patients, three patients discontinued treatment early due to perceived unacceptable side effects, two patients secondary to persistent or relapsing pain, one patient desired pregnancy, and one patient was lost to follow-up. The most commonly cited side effects were weight gain ($n = 3$), hot flashes ($n = 2$), ovarian cyst development ($n = 2$), fatigue ($n = 2$), and breakthrough vaginal bleeding ($n = 2$). Also noted were insomnia ($n = 1$), mood changes and irritability ($n = 1$), acne ($n = 1$), and breast tenderness ($n = 1$). The majority of patients who initiated treatment continued through the recommended 6-month course, and treatment was generally well tolerated.

Pain scores were assessed at every visit and sometimes through telephone encounters. We collected all available pain scores and the dates they were reported. The median pain score at the start of therapy was 7, and at the end of therapy 1.5 (Table 3). Only 9 patients had a follow-up visit after discontinuing treatment. The median of the available pain scores at the follow-up visit was 4.7. Using a two-tailed signed rank test, we found a statistically significant decrease in the median pain score from the start of therapy to the end ($P = .0001$). When comparing follow-up to start using the same test, there was a trend toward a lower pain score; however, there was no statistically significant difference in pain scores between the start of treatment and the follow-up visit ($P = .19$). This finding suggests that pain levels returned to baseline after the treatment was discontinued.

The average ($\pm$ SEM) length of therapy was 180 ± 31 days. Using the Spearman correlation coefficient, there was no correlation (correlation = -0.19 , $P = .49$) between the length of treatment (start to end) and the overall change in pain score (start to end). In the nine patients who presented for a follow-up visit after completing AI treatment, the increase in pain score (end to follow-up) did not correlate (correlation = 0.21 , $P = .59$) with the time interval between the end of the treatment and the follow-up visit (end to follow-up) (Table 4).

Two patients underwent a hysterectomy and bilateral oophorectomy 7 and 17 months after discontinuing treatment with AI. The first patient reported no pain 9 months after surgery, and the second reported a pain score of 2 at 7 months after surgery.

Two patients conceived 2 and 5 months after discontinuing treatment with letrozole. One patient had an uncomplicated pregnancy and a healthy child, whereas the other pregnancy was ongoing without complications at the completion of the study period.

DISCUSSION

Letrozole significantly improved patients' pain scores during the course of treatment. As with other commonly used therapies, such as GnRH agonists, pain recurred after letrozole treatment was discontinued (17). This speaks to the known characteristic of endometriosis as a chronic recurring disease.

Each patient in our study had previously failed at least two conventional therapies before initiating treatment with an AI, representing a group of patients with severe disease that is highly refractory to treatment. Two patients, who initially responded to letrozole,

subsequently underwent hysterectomy and oophorectomy shortly after pain recurrence, implying that AI therapy represented a “last resort” before radical treatment. These patients gained an additional 1–2 years of symptom improvement before resorting to oophorectomy, and their improvement in pain likely contributed to a temporary but not negligible improvement in quality of life. Future studies are needed to determine whether AI treatment improves quality of life indicators, even if patients ultimately require radical surgical treatment. In addition, although AIs are currently used as second- or third-line therapy in patients refractory to conservative management of endometriosis, the use of AIs as first-line therapy for a new diagnosis of endometriosis needs to be evaluated.

In our study we observed three types of responses to letrozole. One group of patients had a complete or near-complete response during AI treatment followed by recurrence after discontinuation of therapy. Another group of patients initially responded but reported relapsing pain symptoms while taking AI, and the third group did not respond to therapy with AIs. Large studies analyzing molecular, demographic, and psychological differences would be necessary to identify characteristics that could permit selection of treatment candidates most likely to benefit from AI.

Pelvic pain due to endometriosis can manifest as chronic continuous pain, dysmenorrhea, or dyspareunia. Given the nature and limitations of our study, we were unable to expound on the impact of AI on different types of endometriosis-related pain in individual patients. In addition, because patients were evaluated at different time intervals, we were unable to accurately compare the time of response and the time of pain recurrence after therapy.

Although adhesion-related pain may have contributed to chronic pain, all patients in this study had undergone at least one laparoscopic procedure for diagnostic or therapeutic purposes and the majority of patients who received prolonged therapy with letrozole had also undergone at least one laparotomy before treatment. The study participants were relatively homogeneous in their prior surgical history and thus we did not evaluate the correlation between prior surgical interventions with response to AIs.

Our findings are consistent with a prospective trial by Ferrero et al. (18) in which 82 women with pain secondary to rectovaginal endometriosis received letrozole and norethisterone acetate or norethisterone acetate alone for 6 months. Pain intensity and deep dyspareunia were significantly lower in the letrozole group at 3- and 6-month intervals after initiating therapy. Similar to our findings, patients reported recurrence of pain symptoms after completing treatment and at a 6-month follow-up visit. A large randomized, double-blinded study by Soysal et al. (14) compared administration of goserelin plus anastrozole to goserelin alone after surgery in 80 patients with severe endometriosis, demonstrating a significantly longer time to symptom recurrence in women who received goserelin plus anastrozole versus goserelin alone (>24 months vs. 17 months). Amsterdam et al. (19) used anastrozole and the combination OC Alesse to achieve significant pain relief in 14 of 15 patients with endometriosis refractory to multiple medical and surgical treatments, and in a prospective study (20) of 12 women with stage 4 endometriosis, patients reported significant improvement in dysmenorrhea and dyspareunia with a combination of letrozole and desogestrol.

The majority of studies published to date have used AIs for a limited treatment course of 6 months. We recommend a similar initial duration of therapy. A longer duration of therapy, however, should be considered in patients who have responded favorably and are motivated to continue therapy. Studies are needed to further elucidate minimum effective dosages, the ideal length of therapy, the role of long-term maintenance therapy, and the use of combination therapies with either OCs or GnRH agonists.

Although we did not perform a cost-effectiveness analysis, we determined based on 2011 prices in Chicago, Illinois, that the cost of treatment with letrozole and norethindrone acetate for a 6-month period would total \$3,443.88 without insurance coverage. A recent study by Guzick et al. (21) suggested that the cost of leuprolide acetate (LA) depot plus norethindrone acetate significantly exceeded the cost of treatment with OC pills alone with no significant improvement in symptoms. Future studies are needed to determine the cost effectiveness and accessibility of AIs for the treatment of severe endometriosis.

A placebo effect cannot be ruled out in our study or in any of the previously published studies and reports. Further randomized controlled studies are needed to evaluate the efficacy of AI.

Future studies are necessary to determine pregnancy rates (PR) after long-term AI treatment for endometriosis. In a prospective randomized clinical trial by Alborzi et al. (22), PRs and recurrent endometriosis rates were compared between women with endometriosis undergoing therapy with an AI (letrozole), a GnRH agonist (triptorelin), or no therapy. There was no difference in PR or endometriosis recurrence among the three groups, but patients were treated for only 2 months.

Our study and previously published studies suggest that endometriosis responds favorably to treatment with AI. Aromatase inhibitors are well tolerated by patients and may represent a promising new therapy for endometriosis. Further evaluation and development is needed to elucidate the role of AI in the management of endometriosis-related pelvic pain.

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TABLE 1

Patient characteristics

Patient characteristic	No. of patients (%) ^a
Gravidity 0	9 (56.0%)
Gravidity 1	7 (44.0%)
Parity 0	13 (81.0%)
Parity 1	3 (19.0%)
Postmenopausal	2 (12.5%)
Premenopausal	14 (87.5%)
Co-existing medical conditions	
Irritable bowel syndrome	4
Depression	3
Fibromyalgia	2
Bipolar affective disorder	2
Hypertension	2
Asthma	2
Co-existing gynecological conditions	
Ovarian cysts	3
Uterine fibroids	1
Median age at presentation (y) (range)	28 (16–45)
Median age at diagnosis of endometriosis (y)	19 (11–34)
Median time between diagnosis and presentation (y)	7 (1–28)
Median age of menarche (y)	12 (9–15)

^a Percentages calculated based on the total number of patients under-going treatment with aromatase inhibitor (n = 16).

TABLE 2

Previous treatments for endometriosis.

Treatment^a	No. of patients (%)
Oral contraceptives	16 (100.0)
Laparoscopy	16 (100.0)
GnRH agonists	10 (62.5)
Medroxyprogesterone acetate	5 (31.0)
Hysterectomy, bilateral salpingo-oophorectomy	3 (8.0)
Laparotomy	1
Danazol	1
Neurostimulation	1

^a Each patient had failed at least two conventional therapies before initiating aromatase inhibitor treatment.

TABLE 3

Pain scores throughout therapy.

	No. of patients	Mean	Median	Range	SEM
S ^a	16	6.8	7.0	3.5–9	0.4
E ^a	16	2.7	1.5	0–9	0.8
F ^b	9	4.7	5.0	0–9	1.3
S–E	16	4.1	5.0	0–8 ^c	0.6
E–F	9	3.0	2.5	–2–9 ^c	1.3
S–F ^b	9	1.7	0	–1.5–6.5 ^c	1

Note: Data were analyzed using a two-tailed Wilcoxon signed rank test. SEM = standard error of the mean.

^aWe found a statistically significant decrease in the median pain score from the start of therapy (S) to the end of therapy (E), $P= .0001$.

^bWhen comparing pain scores at the follow-up visit (F) to the start of therapy (S), we found no statistically significant difference in pain scores, $P= .19$.

^cThese numbers represent a range of change in pain score and not a number on the visual analogue scale. A negative value indicates that, in some patients, pain increased.

TABLE 4

Time intervals from the start of therapy (days).

	No. of patients	Mean	Median	Range	SEM
S-E ^a	16	180	157	35–440	31
S-F	9	513	588	123–743	72
E-F ^b	9	325	277	56–642	60

Note: Data were correlated with change in pain score using Spearman correlation coefficients. SEM = standard error of the mean.

^aWe did not find any correlation ($r = -0.19$, $P = .49$) between the length of treatment (S to E) and the overall change in pain score (S–E). S = start; E = end.

^bIn the nine patients who presented for a follow-up visit after completing aromatase inhibitor treatment, the increase in pain score (E–F) did not correlate ($r = 0.21$, $P = .59$) with the time interval between the end of the treatment and the follow-up visit (E–F). F = follow-up visit.