Role of Aromatase Inhibitors in the Treatment of Endometriosis

Endometriozisin Tedavisinde Aromataz İnhibitörlerinin Yeri

Endometriozs / Endometriosis

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Özet

Endometriozis kronik bir jinekolojik hastalıktır. Uterin kavitede oluşan ektopik glandler ve stroma olarak tanımlanır. Endometriozis sebepli ağrıyı tedavi etmek için bazı hormonal yaklaşımlar ortaya konmuştur. Bu hormonal yaklaşımların temel prensipi overdeki östrojen üretimini engellemesidir. Ancak, bu hormonal tedavileri kullanan hastaların bazılarında gene de ağrı devam etmektedir. Endometriozis esnasında protein ekspresyonu, enzim aktivitesi ve transkripsiyonal ekspresyon seviyelerinde aromataz aktivite bulunmaktadır. Bu sebeple, birçok araştırmacı enodmetriozis tedavisinde aromataz inhibitörlerinin (AI) potansiyel kullanımını değerlendirmektedir. Bu derlemenin amacı endometriozis tedavisinde aromataz inhibitörlerinin rolüne ve bu inhibitörlerin kullanımının klinik açılımlarına ışık tutmaktır.

Anahtar Kelimeler

Aromataz İnhibitörleri; Endometriozis; Pelvik Ağrı

Abstract

Endometriosis is a chronic gynecologic disease that is defined by the existence of ectopic glands and stroma outside the uterine cavity. Some hormonal therapies have been suggested to treat pain that is caused be endometriosis. The basic premise behind these hormonal therapies is that they inhibit the production of estrogens in the ovary. However, some patients can still suffer from pain despite the usage of these conventional hormonal therapies. Aromatase activity is involved in the levels of protein expression, enzyme activity and transcriptional expression in endometriosis. Hence, several researchers have investigated and evaluated aromatase inhibitors (AIs) as a potential treatment option for endometriosis. The aim of this review is to evaluate the role of aromatase inhibitors in the treatment of endometriosis.

Keywords

Aromatase Inhibitors; Endometriosis; Pelvic Pain

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Introduction

Endometriosis is a chronic gynecologic disease that is defined by the existence of ectopic glands and stroma outside the uterine cavity. It affects nearly 3.6% of women and may cause infertility as well as pelvic pain (i.e. dysmenorrhea, deep dyspareunia, chronic pelvic pain and dyschezia) [1]. Symptoms of pain can range from mild to extremely severe. In patients with extreme pain, quality of life and sexual life may be negatively affected [2-4]. Some hormonal therapies have been suggested to treat pain that is caused be endometriosis. These include oral contraceptive pills and drugs with estroprogestin (i.e. vaginal ring, transdermal patch, etc.), progestins (i.e. medroxyprogesterone acetate, norethisterone acetate, levonorgestrel-releasing intrauterine device, etc.), gonadotropin releasing hormone (GnRH) analogues and danazol [5]. The basic premise behind these hormonal therapies is that they inhibit the production of estrogens in the ovary. This is a reasonable approach because of the role of estrogen in stimulating endometriotic tissues and the in situ presence of aromatase in these tissues. However, some patients can still suffer from pain despite the usage of these conventional hormonal therapies.

Estrogens play a vital role in endometriosis by inducing the growth and invasion of endometriotic tissues and prostaglandins, which intermediate pain, infertility, and inflammation by stimulating COX-2 enzyme expression. Subsequently, prostaglandin E2 (PGE2) levels levels elevate, which stimulates aromatase activity in endometriosis [6]. Aromatase activity is involved in the levels of protein expression, enzyme activity and transcriptional expression in endometriosis [2,7-8]. Hence, several researchers have investigated and evaluated aromatase inhibitors (AIs) as a potential treatment option for endometriosis [9-13].

The aim of this review is to evaluate the role of aromatase inhibitors in the treatment of endometriosis.

Aromatase Expression in Endometriotic Tissue

Noble et al. published the first study on expression of aromatase in peritoneal endometriotic tissues in 1996 [1]. They concluded that both eutopic endometrial tissues and endometriotic implants from patients with endometriosis are biochemically different from normal endometrial tissues of healthy women. Since then, several researchers have reported aromatase expression and cellular localization in endometriotic tissue [2-5,14-16] and in eutopic endometrium of women with endometriosis [2,3,5,14-21]. In an earlier study, Kitawaki et al. tried to determine whether estrogen production takes place in endometriotic tissues of eutopic endometrium from patients with endometriosis and in normal endometrium of healthy controls [2]. The authors concluded that endometriotic tissues produce estrogens at a local level. In a prospective study Matsuzaki et al. investigated mRNA expression of aromatase and 17beta-hydroxysteroid dehydrogenase type-2 (17betaHSD2) in epithelial and stromal cells from eutopic and ectopic endometrium of patients with deep endometriosis and reported that aromatase mRNA expression was significantly higher in epithelial cells than in stromal cells in both eutopic and ectopic endometrium obtained from endometriosis patients [3]. In a similar study, Heilier et al. observed that ovarian endometriosis exhibits an 8-fold higher expression of aromatase compared with peritoneal endometriosis, which suggests that aromatase inhibitors may be particularly active in this form of endometriosis [4]. Findings of a study by Velasco et al. confirmed the presence of aromatase activity in endometriosis and probably the existence of a local estrogen production that may be stimulated by some factors such as cytokines present in the peritoneal fluid of these patients [5]. Smuc et al. examined the mRNA levels of six enzymes that are implicated in human ovarian endometriosis and involved in the metabolism of estrogen and progesterone--aromatase: 17beta-hydroxysteroid dehydrogenase (17beta-HSD) types 1, 2 and 7; sulfatase and sulfotransferase; and of the steroid receptors, estrogen receptors alpha and beta (ERalpha, ERbeta) and progesterone receptors A and B (PRAB) [14]. The researchers reported that upregulation of aromatase and upregulation of 17beta-HSD types 1 and 7 and sulfatase may increase the local estradiol concentration. In a prospective study, Acien et al. reported major severity, activity, and chronic pelvic pain in patients with aromatase in endometriotic tissue [15]. Hudelist et al. analyzed the expression of aromatase and E2-inactivating estrogen sulfotransferase (EST) in paired biopsies obtained simultaneously from the endometrium and from endometrial lesions of patients with peritoneal or ovarian endometriosis and in cycling endometria from women without endometriosis [16]. They reported elevated aromatase expression in endometriotic glands in comparison with corresponding uterine endometria. The difference was even more pronounced when uterine endometria from endometriosis patients were compared with those of healthy controls. In a retrospective study, Kitawaki et al. reported detection of aromatase cytochrome P-450 specimens obtained from patients with endometriosis, adenomyosis, and/or leiomyomas but not in specimens obtained from healthy women [18]. In a similar study by Dheenadayalu et al., pelvic endometriosis was strongly associated with aromatase P450 mRNA expression in eutopic endometrium [20]. Kyama et al. examined mRNA expression of aromatase, cytokines, and adhesion factors in women with and without endometriosis, and concluded that endometrium and peritoneum are both involved in the pathogenesis of endometriosis due to aberrant mRNA expression of aromatase, cytokines and adhesion factors in these tissues [21]. In summary, the findings of the above mentioned studies suggest that aromatase mRNA could be detected in endometriotic tissue and/or eutopic endometrium. It is interesting to note that aromatase expression was usually significantly greater in epithelial cells in comparison with stromal cells in these studies. However, in a study by Colette et al. only low levels of aromatase expression were found in ovarian endometriomas, while no expression of aromatase was detected in endometriotic tissue and/or eutopic endometrium [22]. The authors concluded that the aromatase expression in ovarian endometriomas may be a result of ovarian tissue 'contaminating.' This theory may help explain the discrepancy between the findings of Colette et al. [22] and previous studies. On the other hand, a study by Izawa et al. reported that endometriotic stromal cells secrete estrogen [23]. Increased aromatase expression was reported in the cultures of endometriotic cells, which was associated with the epigenetic modifications of the aromatase gene.

Zeitoun et al. may have published the first study on molecular alterations of endometriotic stromal cells and how they result in abnormal production of aromatase [24]. The researchers reported that stimulatory transcription factor (SF-1) was significantly over-expressed in endometriotic stromal cells in comparison with eutopic endometrium stromal cells. In addition, transcription inhibitory factor (COUP-TF) was expressed in eutopic endometrium stromal cells, but was not expressed

in stromal cells from endometriotic tissue. Hence, the authors concluded that over-expression of SF-1 and no expression of COUP-TF caused expression of aromatase and local estrogen production in endometriotic stromal cells.

In summary, the widely-accepted notion of elevated aromatase expression in endometriotic tissue has led many researchers to study AIs as a potential treatment option of endometriosis.

Use of Aromatase Inhibitors in the Medical Treatment of Endometriosis

Anastrozole

Anastrozole is a non-steroidal aromatase inhibitor that competes for binding on the endogenous aromatase enzyme by mimicking normal enzyme substrate [25].It has been used primarily for the treatment of breast cancer after surgery. However, as AIs come under the spotlight as a potential treatment for endometriosis, additional interest has been aroused.

Takayama et al. published the first study, which was a case-report, on the use of anastrozole in the treatment of endometriosis in 1998 [26]. The researchers administered anastrozole (1 mg/day) and elemental calcium (1.5 g/day) for 9 months and alendronate (a nonestrogenic inhibitor of bone resorption, 10 mg/day) was added to this regimen in a patient who presented with an unusually aggressive case of recurrent postmenopausal endometriosis after undergoing hysterectomy and bilateral salpingo-oophorectomy. The result of the treatment was a reduction in pain as well as endometriosis lesion size. In a two-case series, Shippen and West administered anastrozole combined with progesterone (200 mg/day), calcitriol (1.0 mcg/day) and rofecoxib (12.5 mg/day) for 28-day cycles and repeated this six times in patients with severe endometriosis and pain [27]. The results were a progressive reduction in pain and endometriotic lesions over 3 months of treatment in both cases and they became pregnant after one year of treatment. In another study by Amsterdam et al., with a larger group of patients, patients received anastrozole (1 mg/day) along with ethinyl estradiol (20 mcg/day] and levonorgestrel (0.1 mg/day] for six months [10). After one month of treatment, symptoms of pain were significantly reduced. Anastrozole in combination with oral contraceptives might be an interesting alternative in patients who do not respond well to conventional therapies and who do not wish to conceive.

Combining anastrozole with GnRH analogues has also been studied. In a randomized controlled trial by Soysal et al., patients with endometriosis-related pain, either received anastrozole (1 mg/day] plus goserelin (3.6 mg/day] or goserelin (3.6 mg/day] alone for 24 weeks [28). Combination of anastrozole and goserelin significantly increased the pain-free period and decreased the recurrence rate of symptoms.

Anastrozole has also been used in the treatment of rectovaginal endometriosis. In a non-randomized pilot study by Hefler et al., patients with rectovaginal endometriosis received vaginally anastrozole (0.25 mg anastrozole/day] for six months [29]. Although dysmenorrhea, physical and social functioning improved, chronic pelvic pain and dyspareunia did not improve during the therapy. In a more recent study by Verma and Konje [30], patients were treated with anastrozole or letrozole for six months. The treatment was combined with calcium 1.5 g per day and vitamin D 800 U per day. There was a significant reduction in pelvic pain after treatment in all patients. The most common adverse effect was irregular bleeding with anastrozole and joint pain with letrozole.

The studies mentioned above suggest that anastrozole may be an interesting treatment option for premenopausal patients with chronic pelvic pain.

Letrozole

Similar to anastrozole, letrozole is also a non-steroidal aromatase inhibitor that competes for binding on the endogenous aromatase enzyme by mimicking normal enzyme substrate [23]. It has also been used for treatment after breast cancer surgery. The first study in the literature that used letrozole in endometriosis patients was by Ailawadi et al. in 2004 [31]. In this non-randomized prospective study, patients received letrozole (2.5 mg/day), the progestin norethisterone acetate (2.5 mg/day), calcium citrate (1250 mg/day), and vitamin D (800 IU/day) for six months. The combined treatment resulted in a significant reduction of pelvic pain. In a non-randomized study, Ferrero et al. administered either a combination of letrozole and norethisterone acetate or norethisterone acetate alone for 6 months to patients with rectovaginal endometriosis [32]. There was a significant reduction in pelvic pain and dyspareunia symptoms in both groups after 3 months of treatment. After 6 months of period, the symptoms were significantly reduced in the group that was treated with letrozole and norethisterone acetate in comparison with the group that only received norethisterone acetate, but letrozole caused a higher incidence of adverse effects. In addition, after the treatments were ended, symptoms recurred in both groups. The authors concluded that AIs should be reserved for patients with endometriosis that does not respond well to conventional treatments and choose not to undergo surgical management.

In another study by Ferrero et al. patients with bladder endometriosis received letrozole (2.5 mg/day), norethisterone acetate (2.5 mg/day), elemental calcium, and vitamin D3 for 6 months [33]. Pain and urinary symptoms were significantly reduced. In another study by Ferrero et al., patients with colorectal endometriosis received letrozole (2.5 mg/day) and norethisterone acetate (2.5 mg/day) for six months [34]. Symptoms of pain, dyspareunia, dyschezia, cramping and bloating were significantly reduced after six months of treatment. Lall Seal et al. administered letrozole (2.5 mg/day) along with desogestrel (0.15 mg/day), ethinyl estradiol (0.03 mg/day), calcium (1200 mg/day), and vitamin D3 (800 IU/day) to patients with recurrent ovarian endometriomas [35]. Endometriomas disappeared after six months of treatment. However, it is important to note that these studies [33-35] had small sample sizes, which negatively affected the statistical power and subsequently limited the generalizability.

More recently, Abushain et al. administered letrozole (2.6mg/day) along with norethisterone acetate (2.5mg/day) or letrozole (2.5mg/day) along with oral contraceptive pills to patients with endometriosis who did not respond to conventional medical and/or surgical treatments [36]. The pain symptoms of the patients were significantly reduced. However, pain recurred after completing the treatment.

There are case reports in the literature that utilized letrozole by itself [37] or in combination with different steroids [37-39] to treat pain in patients with endometriosis. Razzi et al. administered letrozole (2.5mg/day) to a patient with recurrent endometriosis who had undergone subtotal hysterectomy and bilateral oophorectomy [37]. Symptoms of pelvic pain and dyspareunia were significantly reduced after 6 months of treatment. Fatemi et al. administered letrozole by itself (2.5mg/day) along with pro-

gestin to a postmenopausal patient with recurrent endometriosis (38). Symptoms of pain and dyspareunia were significantly reduced, while the endometrioma almost completely regressed. A similar treatment was used in a patient with endometriosis and severe pain who had undergone hysterectomy and bilateral salpingo-oophorectomy by Mousa et al. [39]. Again, there was significant reduction in pain. Recently, Sasson and Taylor administered letrozole (5 mg/day) along with medroxyprogesterone acetate (10 mg/day) to a postmenopausal patient with a large and recurrent endometrioma [40]. The patient responded well to the treatment. Unfortunately, case reports are difficult to generalize because of inherent subjectivity and because they are based on qualitative subjective data.

There are studies in the literature in which patients did not respond well to the letrozole treatment. For instance, Remorgida et al. carried out a prospective study in 2007 in which they treated endometriosis with letrozole (2.5 mg/day) along with norethisterone acetate (2.5 mg/day) [41]. Initially, symptoms were significantly reduced, especially in patients with rectovaginal endometriosis. However, after the completion of the treatment, pain had recurred at the three-month follow up. As a result, nearly half of the patients underwent surgical management. Postoperative histologic evaluation revealed active endometriotic lesions. In another prospective study, Remorgida et al. administered letrozole (2.5 mg/day) along with desogestrel (75 mcg/day) elemental calcium 1000 mg/day and vitamin D 880 IU/day for six months to patients with stage IV refractory endometriosis [42]. Patients could not complete the treatment as they all developed ovarian cysts. Interestingly, all of the patients reported a significant reduction in symptoms of dysmenorrhea and dyspareunia at the interruption of treatment, which recurred after ending the treatment. Pain symptoms quickly recurred at the three-month follow up.

Potential Adverse Effects of Aromatase Inhibitors

Unfortunately, many of the available studies in the literature that used aromatase inhibitors for the treatment of endometriosis did not provide a sufficient follow up [10,29,31,43]. Some of the studies that provided follow-up data reported a reoccurrence of symptoms after the completion of the treatment [32,36,41-42]. The severity of the symptoms after the completion of the treatment was similar to the severity before the treatment in these studies. In addition, some patients with persistent symptoms of pain who received AIs presented with rectovaginal nodules and several stromal cells with proliferative activity [41].

Premenopausal women who have previously used progestogens and oral contraceptive pills as conventional treatment may experience potential adverse effects of AIs like arthralgia and myalgia more severely. Therefore, treatment compliance rates with AIs may be negatively affected in this patient group. Consequently, in a recent non-randomized patient preference study by Ferrero et al., although letrozole along with norethisterone acetate administration was found to be more effective in reducing symptoms of pain and dyspareunia than norethisterone acetate administration by itself, due to the higher number of adverse effects, the satisfaction of patients was not improved [32]. Hence, it may be worth considering combining AIs with progestogens rather than gonadotropin releasing hormone analogues. To strengthen this argument, in a recent randomized controlled trial, Ferrero et al. randomized patients with rectovaginal endometriosis to receive either oral norethisterone acetate (2.5 mg/day) or intramuscular injection of triptorelin (11.25 mg every 3 months) for six months [43]. As a result, combining letrozole with oral norethisterone acetate was associated with a lower incidence of adverse effects and a lower discontinuation rate than combining letrozole with triptorelin.

Furthermore, there is the issue of long-term treatment with AIs in premenopausal women. Bone health seems to be affected negatively by third-generation AIs [44,45]. The prevailing theory is that AIs suppress aromatase activity in osteoblasts, which leads to an increase in osteoclastic activity and loss of bone mineral density [44]. The randomized controlled trial of Ferrero et al., which was discussed in detail previously, reported a significant decrease in bone mineral density in patients with rectovaginal endometriosis who were treated with triptorelin [43]. In another study by Park et al, bone mineral density was significantly decreased in premenopausal patients with breast cancer who were treated with AIs [46]. Hypoestrogenism caused by AIs may also have other adverse effects. For example, AIs failed to lower lipid levels and provide a cardioprotective effect like tamoxifen in patients with breast cancer [47]. On the other hand, there was no increased cardiovascular risk observed, yet data specifically on the potential cardioprotective effects of AIs is still very limited in premenopausal women to draw any serious conclusions.

Long-term routine clinical treatment of endometriosis with AIs, particularly in combination with GnRHs, seems unlikely because of the adverse effects, which have been discussed above. On the other hand, combining AIs with other hormonal therapies like norethisterone acetate may reduce the adverse effects such as the decline of bone mineral density. However, treatment with AIs should be reserved for patients who do not respond to conventional hormonal treatments and/or surgical management of endometriosis. Before the initiation of treatment with AIs, endometriosis has to be histologically diagnosed and the bone mineral density of the patient should be normal. As in all such treatments, patients should be well informed about the potential adverse effects of treatment.

Conclusions

The evidence from the currently available literature suggests that aromatase expression is increased in endometriotic issue. This increased aromatase activity seems to trigger local estrogen production and subsequently endometriotic lesion growth. Such endometriotic lesion growths are associated with pelvic pain symptoms in varying levels. Therefore, not surprisingly, the increased aromatase activity via administration of AIs has led to a reduction in endometriotic lesions.

The studies that are discussed in this review mostly document the efficacy of AIs in the short-term treatment of endometriosis. On the other hand, most patients with endometriosis require long-term treatment in which the potential benefits should be balanced with potential adverse effects. Subsequently, efficacy of long-term treatment with AIs remains uncertain due to the persistence of endometriotic lesions and the high rate of adverse effects. In addition, risks of hypoestrogenism related to treatment with AIs should be kept in mind when considering AIs for premenopausal women. For some patients, the higher cost of AIs comparison with conventional hormonal therapies may also be an important factor. In light of the currently available literature, it seems that AIs should be reserved for women with severe pain symptoms who do not respond well to conventional surgical management and/or hormonal therapies.

Further studies are urgently needed to evaluate whether long-

term treatment with AIs is more efficient than conventional therapies that are currently available. Such studies should pay special attention to improvement of pain symptoms, patient satisfaction, and incidence of adverse effects.

Competing interests

The authors declare that they have no competing interests.

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