Endometriosis: *Case Report*

Bazedoxifene–Conjugated Estrogens for Treating Endometriosis

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BACKGROUND: Endometriosis is a gynecologic disorder affecting 6–10% of reproductive-aged women. First-line therapies are progestin-based regimens; however, failure rates are high, often requiring alternative hormonal agents, each with unfavorable side effects. Bazedoxifene with conjugated estrogens is approved for treatment of menopausal symptoms, and use in animal studies has demonstrated regression of endometriotic lesions. As such, it represents a potential treatment option for endometriosis.

CASE: A patient with stage III endometriosis referred for management of dysmenorrhea and cyclic pelvic pain was treated with 20 mg bazedoxifene and 0.45 mg conjugated estrogens daily for more than 6 months. She noted resolution of pelvic pain. There were no abnormal effects on hormonal, uterine, or ovarian parameters.

CONCLUSION: Bazedoxifene with conjugated estrogens may be an effective alternative to traditional endometriosis treatment options.

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Teaching Points

1. The estrogen receptor (ER) is a definitive downstream target in endometriosis. As an endometrial ER antagonist, bazedoxifene assures not only blockade of estrogen binding, but it also has the ability to degrade the receptor. This unique property of bazedoxifene blocks estrogen action and makes it an attractive treatment option for endometriosis.
2. Conjugated estrogens paired with bazedoxifene do not require a progestin to block endometrial growth, thus avoiding the side effects associated with progestin-based regimens.

Endometriosis is a debilitating disorder characterized by the growth of endometrial tissue outside the uterus.[1] Pelvic pain, dyspareunia, and infertility are the most common symptoms of endometriosis that can have a significant effect on patients' lives.[1] Treatment consists of agents that induce atrophy of endometriotic lesions. There is tremendous need for therapies that are effective, have favorable side effect profiles, and can be used long term in women with symptomatic endometriosis, especially for those not responding to progestin-based regimens.

Bazedoxifene with conjugated estrogens is the first Tissue Selective Estrogen Complex approved by the U.S. Food and Drug Administration for treatment of menopausal symptoms.[2,3] Bazedoxifene is a selective estrogen receptor modulator (SERM) that, on binding to the ER, can exert agonist or antagonist effects. In menopausal women, bazedoxifene–conjugated estrogens improves hot flushes, vulvovaginal atrophy, and prevents bone loss with no associated adverse effects on the breast, uterus, or ovary.[3–5] In eutopic endometrium from women with endometriosis, we have previously demonstrated that cells expressing high levels of aromatase responded to bazedoxifene treatment.[6] In a murine model of endometriosis, we have demonstrated that administration of bazedoxifene with or without coadministration of conjugated estrogens resulted in decreased size of endometrial implants.[7,8] Furthermore, there was a uterine ER antagonistic effect in eutopic and ectopic endometrium as well as decreased expression and degradation of ER with treatment of bazedoxifene alone or with conjugated estrogens.[7,8] Given these findings, we hypothesized bazedoxifene–conjugated estrogens would function similarly in premenopausal patients with endometriosis.

CASE

A 36-year-old woman, gravida 0, was referred to our reproductive endocrinology center for management of endometriosis-associated pain. Her surgical history

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included a laparoscopy with excision of endometriosis and removal of an endometrioma. Stage III endometriosis was documented, and histopathology confirmed the diagnosis of endometriosis. She had a medical history of psoriatic arthritis for which she was treated with secukinumab for joint pain, yet she continued to note ongoing dysmenorrhea and cyclic pelvic pain related to endometriosis. She previously used combined oral contraceptives as well as high-dose progestin therapy but reported continued pelvic pain on these regimens. She was subsequently started on depot leuprolide acetate (11.25 mg) with norethindrone (5 mg) add-back therapy. Her pelvic pain improved; however, she represented with bothersome hot flushes. Symptomatic control was attempted with alternative add-back regimens: conjugated estrogens with medroxyprogesterone and estradiol (oral and transdermal) with micronized progesterone; however, she noted continued hot flushes and breakthrough bleeding with associated pain. She also noted decreased libido. She was offered bazedoxifene–conjugated estrogens after reviewing potential risks as well as the lack of efficacy data using this regimen for endometriosis. Given the menopausal dose of estrogen in bazedoxifene–conjugated estrogens, she was counseled on the need for barrier contraception. She signed an informed consent form and agreed to publication of this report; the institutional review board approved of this treatment.

The patient had discontinued leuprolide acetate and add-back therapy 5 months prior and had resumed cycling at the time of initiation of bazedoxifene–conjugated estrogens. Treatment with bazedoxifene–conjugated estrogens, one tablet (20 mg bazedoxifene and 0.45 mg conjugated estrogens) daily, began in the early follicular phase. Serum hormonal levels, including follicle-stimulating hormone (FSH), luteinizing hormone, estradiol, and progesterone, were measured three times in each cycle for the first 2 months of therapy. She also underwent transvaginal ultrasonography to assess endometrial thickness, ovarian volume, and ovarian cyst or follicle formation. She completed a clinical symptom survey at each clinical visit in which she was asked a series of questions regarding potential changes in her menstrual cycles, including length, flow, menstrual symptoms, and cycle frequency. Blood samples, ultrasonography, symptoms, and potential side effects were assessed during the early follicular phase, late follicular phase, and midluteal phase of the menstrual cycle. There were no adverse effects on hormonal parameters, uterine, or ovarian morphology. Follicle-stimulating hormone levels remained nearly constant throughout the menstrual cycle, luteinizing hormone levels varied, and estradiol and progesterone levels demonstrated cyclic changes (Table 1). Endometrial thickness was never abnormal (average thickness 4.2 mm), and no abnormal ovarian cysts developed. Before starting any hormonal therapy, the patient reported painful menses lasting 7 days with heavy flow, requiring oxycodone with acetaminophen for pain control. Since starting bazedoxifene–conjugated estrogens, she noted decreased flow and duration of menses and resolution of pelvic pain. Specifically, she noted menses lasting only 3 days that were light; she never required narcotics for dysmenorrhea, and she did not experience breakthrough bleeding. Of note, while on leuprolide acetate with add-back therapy, she had noted low libido; however, while taking bazedoxifene–conjugated estrogens, she noted an increased libido. She has continued on this regimen for more than 6 months and reports satisfaction, including normal menstrual cramping without pain.

Table 1. Reproductive Hormones

	Cycle Phase		
Hormone	Early Follicular	Late Follicular	Midluteal
FSH (milli-international units/mL)	10	10	7
LH (milli-international units/mL)	7.5	12	5
Estradiol (pg/mL)	46.5	181	90
Progesterone (ng/mL)	0.05	1	7

FSH, follicle-stimulating hormone; LH, luteinizing hormone.

DISCUSSION

Although the etiology of endometriosis remains largely unknown, the role of estrogens in the development and growth of endometriosis is well characterized.[1] Women with endometriosis can become nonresponsive to progestin-based therapy as a result of progestin resistance or to gonadotropin-releasing hormone (GnRH) analogs as a result of aromatase expression in lesions.[9] In addition to the progesterone-resistant phenotype, progesterone receptor gene polymorphisms can also affect risk of endometriosis development. The *PROGINS* polymorphism can affect ligand binding and downstream signaling in endometriosis, and individuals with this polymorphism are at increased risk of endometriosis.[10] With respect to GnRH analogs, decreased FSH production resulting from treatment will suppress ovarian estradiol production but will not inhibit local estrogen production by aromatase in endometriotic lesions.[1] Aromatase inhibitors can therefore help prevent endometriosis progression by lowering estrogen concentrations, but must be given with an oral contraceptive, progestin, or GnRH analog to prevent an increase in FSH and stimulation of follicular development.[9,11] Despite suppression of systemic and peripheral estrogen production by existing therapies, endometriotic lesions may still produce sufficient amounts of estradiol to promote ectopic growth.[11] The estrogen receptor is a downstream target in endometriosis. As an endometrial ER antagonist, bazedoxifene assures not only blockade of estrogen action, but

it also has the ability to degrade the receptor. This unique property of bazedoxifene prevents the possibility of estrogen action and makes bazedoxifene an attractive treatment option.

Not all SERMs paired with conjugated estrogens function in the same way. Administration of conjugated estrogens with the SERM raloxifene results in proliferation of the endometrium.[12] In a randomized placebo-controlled trial using raloxifene for the treatment of pelvic pain in women after surgical excision of endometriosis, there was a shortened time for return of pain compared with placebo.[13] Bazedoxifene is structurally and mechanistically distinct from other SERMs.[14,15] The addition of conjugated estrogens to bazedoxifene is hypothesized to provide negative feedback in the central nervous system, inhibiting the increase in FSH (and potential ovarian cyst formation). However, given bazedoxifene's uterine specificity, it exhibits less antiestrogenic effects in the brain, diminishing the likelihood of gonadotropin release and resultant ovarian stimulation.[7] Equally important, conjugated estrogens paired with bazedoxifene do not require a progestin to block endometrial growth,[14] thus avoiding the side effects associated with progestin-based regimens. The most commonly reported side effects of bazedoxifene–conjugated estrogens include muscle spasms, nausea, diarrhea, abdominal pain, oropharyngeal pain, dizziness, and neck pain.[16] It is also important to recognize the U.S. Food and Drug Administration box warnings for bazedoxifene–conjugated estrogens, which note increased risk of endometrial cancer in women with a uterus using unopposed estrogens; estrogen therapy should not be used for the prevention of cardiovascular disease; the Women's Health Initiative estrogen-alone substudy noted increased risk of stroke and deep vein thrombosis; the Women's Health Initiative Memory Study estrogen-alone ancillary study reported an increased risk of probable dementia in postmenopausal women 65 years of age and older; and not to take additional estrogens with bazedoxifene–conjugated estrogens.[16]

Our patient noted complete resolution of her pain symptoms, where other hormonal agents she had tried in the past had failed. A systematic search in PubMed using the key words "endometriosis and bazedoxifene and conjugated estrogens" yielded no clinical reports of its single use in patients with endometriosis. Although this is one report, we found bazedoxifene–conjugated estrogens use was safe and well tolerated with no adverse effects on measured parameters. Given that our patient continued to ovulate, as evidenced by progesterone levels as well as patient-reported monthly menses while on bazedoxifene–conjugated estrogens, it is imperative to counsel patients on the need for reliable contraception. Although our findings in a single patient are provocative, bazedoxifene–conjugated estrogens for endometriosis-associated pelvic pain need to be further tested to determine the efficacy and safety profile.

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