Clinical Case Reports

Open Access

CASE REPORT

Bazedoxifene/conjugated estrogens in combination with leuprolide for the treatment of endometriosis

Amanda M. Hill[1], Bruce Lessey[2], Valerie A. Flores[1] & Hugh S. Taylor[1]

[1]Yale School of Medicine, Yale New Haven Health, New Haven, Connecticut
[2]Fertility Center of the Carolinas, Greenville Health System, Greenville, South Carolina

Correspondence
Hugh S. Taylor, Yale School of Medicine, Yale New Haven Hospital, 333 Cedar Street, New Haven, 06520 CT. Tel: (203) 785-4001; Fax: (203) 785-4713; E-mail: hugh.taylor@yale.edu

Funding Information
No sources of funding were declared for this study.
Received: 30 November 2017; Revised: 14 February 2018; Accepted: 28 February 2018

***Clinical Case Reports* 2018; 6(6): 990–994**

doi: 10.1002/ccr3.1501

Key Clinical Message

Bazedoxifene/conjugated estrogens can be used with leuprolide as effective add-back therapy in premenopausal women with endometriosis without unwanted stimulation of the breasts, CNS (Central Nervous System), or endometrium. Bazedoxifene/conjugated estrogens may be an effective progestin-free alternative to traditional add-back therapies.

Keywords

Bazedoxifene, endometriosis, pelvic pain, SERMs.

Introduction

Endometriosis is a chronic, often disabling disease characterized by endometrial tissue outside of the uterine cavity [1, 2]. Patients suffer from pelvic pain, dysmenorrhea, and infertility as a result of endometriosis [1, 2]. Endometriosis occurs in the reproductive-aged population, often presenting in adolescence and persisting through menopause [1, 2].

Current treatments for pain caused by endometriosis are suboptimal and consist of NSAIDs and hormonal modalities [3–9]. Endometriosis is thought to be hormone-responsive and similar to eutopic endometrium. Estrogens drive the growth of endometriosis, while progestins cause differentiation, decidualization, and prevent proliferation. Hormonal treatments aim to decrease the effect of estrogen through pseudopregnancy or pseudomenopause. Unfortunately, endometriosis is often resistant to progestin therapy and progestin therapy often fails. Endometriosis may express aromatase, thereby generating high local estrogen concentrations and negating the effects of ovarian suppression.

Continuous combination oral contraceptives are typically the first-line treatment, but have a high failure rate and frequent side effects including gastrointestinal discomfort and breakthrough bleeding [4, 6, 7]. Treatment with progestins alone also has a high failure rate and can cause unpleasant side effects such as bloating, breast tenderness, irregular bleeding, and mood changes [4, 6]. Gonadotropin-releasing hormone (GnRH) agonists are a more effective treatment of endometriosis and result in pseudomenopausal symptoms which can be debilitating, especially in a young woman [8, 9]. Chronic use can also lead to osteopenia, necessitating hormonal add-back therapy with progestins, which can then lead to other problems including breast tenderness and abnormal bleeding [10].

This case series demonstrates the use of bazedoxifene with conjugated estrogens (BZA/CE) with leuprolide for the treatment of endometriosis in reproductive-aged women. While BZA/CE was used as "add-back" hormone therapy concomitantly with a GnRH agonist, there is likely an independent treatment effect of BZA on endometriosis.

Cases

Case 1

A 21-year-old G0 was referred to Reproductive Endocrinology for treatment of endometriosis. She reported constant pelvic pain, worse with menses, and dyspareunia. Oral contraception pills did not relieve her symptoms. She had a history of surgical resection of endometriosis and was placed on leuprolide postoperatively. She was unhappy with the menopausal side effects of leuprolide and did not continue therapy. She had also tried progestin therapy in the past but had severe mood disturbances. Her pain continued to be a major problem in her life and sought alternative treatment.

The patient's past medical history included hypothyroidism and fibromyalgia. In addition to the laparoscopy for endometriosis, she had a thyroidectomy for a multinodular goiter. She was taking levothyroxine, amitriptyline, and NSAIDs. Physical examination and pelvic ultrasound were unremarkable other than tenderness in the rectovaginal septum; abdomen was nontender, and ultrasound revealed normal ovaries with no evidence of endometriosis.

Initial treatment was leuprolide with conjugated estrogen plus medroxyprogesterone add-back therapy. She had an initial flare in her endometriosis pain after her first leuprolide injection (3.75 mg), as well as bothersome irregular uterine bleeding that continued for 6 weeks. Her pain never decreased to an acceptable level. At this point, conjugated estrogen/medroxyprogesterone was discontinued, and she was started on bazedoxifene with conjugated estrogens and was given a 3-month course of leuprolide (11.25 mg). Within 1 month, her bleeding stopped and her pain subsided. Toward the end of the three-month course, her pain flared again, and she was switched back to monthly leuprolide dosing. Endometrial stripe measurement on transvaginal ultrasound at that time was 4 mm. The patient is satisfied with her treatment and has had continued relief for more than 6 months without any unwanted side effects.

Case 2

A 26-year-old woman with long history of pelvic pain and bleeding presented with severe dysmenorrhea and abnormal uterine bleeding. She had tried OCPs at age 17, but the pain continued. She underwent two laparoscopies, the first showing psammoma bodies and the second, which was performed by a gynecologic oncologist, diagnosed endosalpingiosis. Postoperatively, she was administered depo-medroxyprogesterone; however, she bled continuously. She subsequently received leuprolide (11.25 mg) with continued bleeding and severe pain.

She was given a combination of 11.5 mg leuprolide (three-month duration) and bazedoxifene with conjugated estrogens, and the bleeding stopped. She has had recurrent episodes of pain toward the end of the duration of the leuprolide injections, but this was avoided with 2.5-month dosing intervals instead of usual 3 months. She is now completely asymptomatic. After more than 2 years on this regimen, she reports no hot flashes and no bleeding and is attending graduate school.

Case 3

A 26-year-old woman with PCOS was diagnosed with endometriosis by diagnostic laparoscopy. She did not receive adequate pain relief from the surgery and was referred for further management. After failing conventional management with oral contraceptive pills, she was offered leuprolide plus bazedoxifene with conjugated estrogens, which she accepted. She has had complete pain relief and no bleeding for more than 5 months and is hoping to continue on this long term, citing no unwanted side effects.

Discussion

While there is clear evidence that endometriosis is an estrogen-dependent disease, there has been a dearth of methods available to alter estrogen levels effectively to control endometriosis symptoms without unwanted side effects. Oral contraceptive pills have a high long-term failure rate [4, 6, 7]. GnRH agonists cause vasomotor symptoms, vaginal dryness, and bone loss [8–10]. Progestins, used for primary treatment or for "add-back" therapy, cause often unacceptable side effects such as weight gain, breast tenderness, and mood changes [4, 6]. The ideal medical treatment for endometriosis has yet to be identified.

Selective estrogen receptor modulators (SERMs) have variable tissue-specific agonist or antagonist activity. They are used for the treatment of breast cancer and osteoporosis due to the antagonistic effects on the breast and skeletal systems [11]. Some SERMs display antagonistic effects on the endometrium, preventing endometrial proliferation [11]. For this reason, they have been considered for suppression of endometriosis. Unfortunately, the opposite was seen in a randomized trial using raloxifene; subjects assigned to daily raloxifene treatment had more pain than those assigned to placebo [12].

Bazedoxifene (BZA) is a new-generation SERM that has been approved in combination with conjugated estrogens (CE) for the treatment of menopausal vasomotor symptoms [13]. The usual dosing is one tablet daily, containing 0.45 mg of CE and 20 mg of BZA. Bazedoxifene

in combination with conjugated estrogens has the potential to inhibit endogenous estrogen's stimulatory effect on endometriosis, while having favorable effects on the skeletal system and central nervous system, blocking estrogen effects on the endometrium, and avoiding endometrial hyperplasia [14–16]. It also avoids use of other available agents for add-back such as progestins, improving the safety and side effect profile.

The combination of BZA with CE does not affect the endometrium of menopausal women when compared to placebo [15, 16]. This ability to counteract the stimulatory effect of CE in the endometrium suggests that BZA is also a potential candidate to effectively treat endometriosis. The addition of estrogens to BZA may further inhibit endometriosis through feedback inhibition and decreased ovarian stimulation in a premenopausal woman.

Bazedoxifene alone has a protective effect on the skeletal system, maintaining bone mass in postmenopausal women [17–20] and decreasing vertebral fractures over up to 7 years of use [14]. In combination with CE, treatment similarly led to increased bone density compared to placebo [21]. BZA/CE decreases vaginal atrophy, improving maturation index and reducing vaginal symptoms [22]. BZA/CE also has been shown to have an acceptable cardiovascular safety profile, with rates of coronary heart disease and stroke comparable to placebo in a meta-analysis of postmenopausal women taking BZA with CE for up to 2 years [23] as well as improved lipid profiles [24]. Further, BZA/CE did not induce breast tenderness or increase mammographic density as is seen with menopausal hormone therapy, suggesting a neutral or potential beneficial effect on the breast [25]. Finally, BZA/CE has a high amenorrhea rate, avoiding the common occurrence of break through bleeding frequently seen upon initiation of hormone therapy.

In a mouse model, BZA alone or in combination with CE inhibits growth of surgically transplanted intraperitoneal endometrial lesions, reducing many of the lesions to fibrosis or scar [26, 27]. In these models, endometriosis lesions are sutured onto the pelvic sidewall or peritoneal surface. The mice continue to cycle while on treatment, and there is no effect on ovarian weight or cyst formation [26, 27]. Endometrial hyperplasia does not occur, and uterine weights decrease on treatment when compared to controls [26, 27]. Furthermore, treatment with BZA, alone or in combination with CE, results in decreased estrogen receptor expression [26, 27], while treatment with CE alone causes increased expression [27]. BZA/CE also decreases stem cell recruitment by endometriosis lesions in this model, restoring normal stem cell engraftment of the uterine endometrium [28].

The cases presented here demonstrate the safe and effective use of BZA/CE in premenopausal women with endometriosis after medically induced menopause. An additional five patients with endometriosis, ages ranging from 16 to early thirties, were referred to our centers after failing multiple treatment regimens. Each was treated with leuprolide and bazedoxifene with conjugated estrogens, and all had excellent pain relief. All were referred back to their local physician, and therefore, further details about these patients were unavailable.

The use of CE reduces vasomotor symptoms and bone loss associated with GnRH agonists, while the BZA inhibits the stimulatory effect on the endometrium and endometriosis, avoiding exacerbation of symptoms. The use of a progestin add-back is avoided, eliminating the associated side effects and improving patient satisfaction and compliance. The addition of CE decreases FSH production and ovarian stimulation through negative feedback and prevents vasomotor symptoms that are typically experienced with use of SERMs alone. While the use of BZA/CE alone (without GnRH agonists) should theoretically improve endometriosis symptoms, this therapeutic approach has not been investigated in human subjects.

Future directions should include human trials evaluating the use of BZA/CE with and without GnRH agonists for the management of endometriosis. If use of BZA/CE alone is effective, it could eliminate the initial stimulation of endometriosis and symptom flare often experienced by patients treated with GnRH agonists, as well as the concern about long-term use of leuprolide or newer orally active GnRH agonists in young women. Large comparative trials are needed to assess the safety of long-term use of BZA/CE. The ability to suppress endometriosis while maintaining bone health and inhibiting endometrial growth without a progestin makes BZA/CE an ideal agent for the treatment of endometriosis.

Acknowledgments

None.

Conflict of Interest

None declared.

Authorship

AH: wrote the manuscript, performed background research, and involved in direct patient management as a Fellow. BL: supplied patient information, obtained informed consent, edited the manuscript, and performed direct patient management. VF: supplied patient information, obtained informed consent, and edited the

manuscript. HST: supplied patient information, obtained informed consent, edited the manuscript, and performed direct patient management.

References

1. Giudice, L. C., and L. C. Kao. 2004. Endometriosis. Lancet 364:1789–1799.
2. Bulun, S. E. 2009. Endometriosis. N. Engl. J. Med. 360:268–279.
3. Allen, C., S. Hopewell, A. Prentice, and D. Gregory. 2009. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database Syst. Rev. CD004753.
4. Al Kadri, H., S. Hassan, H. M. Al-Fozan, and A. Hajeer. 2009. Hormone therapy for endometriosis and surgical menopause. Cochrane Database Syst. Rev. CD005997.
5. Nawathe, A., S. Patwardhan, D. Yates, G. R. Harrison, and K. S. Khan. 2008. Systematic review of the effects of aromatase inhibitors on pain associated with endometriosis. BJOG 115:818–822.
6. Rodgers, A. K., and T. Falcone. 2008. Treatment strategies for endometriosis. Expert Opin. Pharmacother. 9:243–255.
7. Davis, L., S. S. Kennedy, J. Moore, and A. Prentice. 2007. Modern combined oral contraceptives for pain associated with endometriosis. Cochrane Database Syst. Rev. CD001019.
8. Surrey, E. S. 2010. Gonadotropin-releasing hormone agonist and add-back therapy: what do the data show? Curr. Opin. Obstet. Gynecol. 22:283–288.
9. Divasta, A. D., and M. R. Laufer. 2013. The use of gonadotropin releasing hormone analogues in adolescent and young patients with endometriosis. Curr. Opin. Obstet. Gynecol. 25:287–292.
10. Hornstein, M. D., E. S. Surrey, G. W. Weisberg, and L. A. Casino. 1998. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. Obstet. Gynecol. 91:16–24.
11. Ellis, A. J., V. M. Hendrick, R. Williams, and B. Komm. 2015. Selective estrogen receptor modulators in clinical practice: a safety overview. Expert Opin. Drug Saf. 14:921–934.
12. Stratton, P., N. Sinaii, J. Segars, D. Koziol, R. Wesley, C. Zimmer, et al. 2008. Return of chronic pelvic pain from endometriosis after raloxifene treatment: a randomized controlled trial. Obstet. Gynecol. 111:88–96.
13. Pinkerton, J. V., W. H. Utian, G. D. Constantine, S. Olivier, and J. H. Pickar. 2009. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial [SMART-2]. Menopause 16:1116–1124.
14. Palacios, S., S. L. Silverman, T. J. de Villiers, A. B. Levine, S. Goemaere, J. P. Brown, et al. 2015. A 7-year randomized, placebo-controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: effects on bone density and fracture. Menopause 22:1–8.
15. Pickar, J. H., I.-T. Yeh, G. Bachmann, and L. Speroff. 2009. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. Fertil. Steril. 92:1018–1024.
16. Archer, D. F., J. V. Pinkerton, W. H. Utian, J. C. Menegoci, T. J. de Villiers, C. K. Yuen, et al. 2009. Bazedoxifene, a selective estrogen receptor modulator: effects on the endometrium, ovaries, and breast from a randomized controlled trial in osteoporotic postmenopausal women. Menopause 16:1109–1115.
17. Miller, P. D., A. A. Chines, C. Christiansen, H. C. Hoeck, D. L. Kendler, E. M. Lewiecki, et al. 2008. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. J. Bone Miner. Res. 23:525–535.
18. Silverman, S. L., C. Christiansen, H. K. Genant, S. Vukicevic, J. R. Zanchetta, T. J. de Villiers, et al. 2008. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J. Bone Miner. Res. 23:1923–1934.
19. Christiansen, C., C. H. III Chesnut, J. D. Adachi, J. P. Brown, C. E. Fernandes, A. W. Kung, et al. 2010. Safety of bazedoxifene in a randomized, double-blind, placebo- and active-controlled phase 3 study of postmenopausal women with osteoporosis. BMC Musculoskelet. Disord. 11:130.
20. Beck, T., T. Fuerst, K. Gaither, S. Sutradhar, A. Levine, T. Hines, et al. 2015. The effects of bazedoxifene on bone structural strength evaluated by hip structural analysis. Bone 77:115–119.
21. Pinkerton, J. V., J. A. Harvey, R. Lindsay, K. Pan, A. A. Chines, S. Mirkin, et al. 2014. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J. Clin. Endocrinol. Metab. 99: E189–E198.
22. Kagan, R., R. S. Williams, K. Pan, S. Mirkin, and J. H. Pickar. 2010. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. Menopause 17:281–289.
23. Komm, B. S., J. R. Thompson, and S. Mirkin. 2015. Cardiovascular safety of conjugated estrogens plus bazedoxifene: meta-analysis of the SMART trials. Climacteric 18:1–9.
24. Mirkin, S., K. Pan, K. A. Ryan, A. Chines, and J. C. Stevenson. 2015. A pooled analysis of the effects of conjugated estrogens/bazedoxifene on lipid parameters in postmenopausal women from the selective estrogens,

menopause, and response to therapy (SMART) trials. J. Clin. Endocrinol. Metab. 100:2329–2338.
25. Pinkerton, J. V., J. A. Harvey, K. Pan, J. R. Thompson, K. A. Ryan, A. A. Chines, et al. 2013. Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. Obstet. Gynecol. 121:959–968.
26. Kulak, J., C. Fischer, B. Komm, and H. S. Taylor. 2011. Treatment with bazedoxifene, a selective estrogen receptor modulator, causes regression of endometriosis in a mouse model. Endocrinology 152:3226–3232.
27. Naqvi, H., S. Sakr, T. Presti, G. Krikun, B. Komm, and H. Taylor. 2014. Treatment with bazedoxifene and conjugated estrogens results in regression of endometriosis in a murine model. Biol. Reprod. 90:121, 1–7.
28. Sakr, S., H. Naqvi, B. Komm, and H. S. Taylor. 2014. Endometriosis impairs bone marrow-derived stem cell recruitment to the uterus whereas bazedoxifene treatment leads to endometriosis regression and improved uterine stem cell engraftment. Endocrinology 155:1489–1497.