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Mini review

Perspective on prescribing conjugated estrogens/bazedoxifene for estrogen-deficiency symptoms of menopause: A practical guide

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ABSTRACT

Current guidelines recommend that hormone therapy (HT) in postmenopausal women with a uterus include a progestin to protect against endometrial hyperplasia. However, many concerns relating to HT use appear to be related to the progestin component, including cardiovascular risk, breast stimulation, and irregular vaginal bleeding. Conjugated estrogens (CE) combined with the selective estrogen receptor modulator bazedoxifene (BZA) is a new progestin-free HT option for alleviating estrogen deficiency symptoms in postmenopausal women with a uterus for whom treatment with progestin-containing therapy is not appropriate. Five double-blind, randomized, placebo-controlled, phase 3 studies, known as the Selective estrogens, Menopause, And Response to Therapy (SMART) trials have investigated the efficacy of CE/BZA for relieving vasomotor symptoms (VMS), and effect on bone mass, as well as endometrial and breast safety in postmenopausal women. In a 12-week study, CE 0.45 mg/BZA 20 mg significantly reduced the number and severity of hot flushes compared with placebo at weeks 4 and 12. Unlike estrogen-progestin therapy (EPT), CE 0.45 mg/BZA 20 mg did not increase breast density compared with placebo. In clinical trials up to 2 years, CE/BZA had a favorable tolerability profile, demonstrated by amenorrhea rates similar to placebo. Vascular disorders including venous thromboembolic events (pulmonary embolism, retinal vein thrombosis, deep vein thrombosis, and thrombophlebitis) were rare events, occurring in less than 1 per 1000 patients. CE/BZA was associated with significantly higher incidences of amenorrhea and lower incidences of bleeding compared with CE/medroxyprogesterone acetate in 2 comparative trials. Therefore, CE 0.45 mg/BZA 20 mg provides an effective, well-tolerated, progestin-free alternative to EPT for postmenopausal women with a uterus.

Contents

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1. Introduction

Hormone therapy (HT) is established as the most effective therapy for vasomotor symptoms (e.g., hot flushes, night sweats) in women younger than 60 years [1]. The addition of a progestogen to systemic estrogen (estrogen-progestin therapy [EPT]) is recommended for nonhysterectomized women to prevent endometrial cancer [2]. Many concerns about HT appear to be related to the progestin component, as coronary heart disease risk, increased mammographic breast density, breast cancer risk, breast pain, and irregular vaginal bleeding occur more frequently with EPT than with estrogen therapy (ET) [3–6]. Thus, there is a need for progestin-free treatment options that protect the endometrium, with a clinically evidenced efficacy and improved tolerability/safety profile.

Conjugated estrogens (CE)/bazedoxifene (BZA) (CE/BZA; Duavive®, Duavee®) is a novel tissue selective estrogen complex (TSEC) combining estrogens with a selective estrogen receptor modulator (SERM). The rationale for TSEC development was that the SERM component would minimize adverse estrogenic effects on the endometrium and breast, while maintaining the beneficial effects of estrogens on menopausal symptoms [7]. BZA was specifically selected as this SERM because it showed favorable preclinical effects on the skeleton, vasomotor activity, and lipid metabolism, as well as mammary and uterine safety [8]. Gene expression profiling of CE in combination with 3 different SERMs (BZA, raloxifene, and lasoxifene) showed differential patterns of gene expression, indicating that different SERM/CE combinations may have distinct clinical activities [9]. Preclinical data have shown that whereas CE alone stimulates proliferation of MCF-7 and T47D human breast cancer cells and reduces cell apoptosis, the addition of BZA at an adequate dose level abrogates these effects [10]. In a separate analysis, BZA was also shown to be a more potent inhibitor of CE-dependent in vitro breast cancer cell proliferation than raloxifene and lasoxifene. A phase 3 study of BZA alone in postmenopausal women with osteoporosis demonstrated a favorable long-term safety profile in the endometrium, breast, and reproductive tract over 7 years [11].

2. Efficacy of CE/BZA in phase 3 clinical trials

CE 0.45 mg/BZA 20 mg once daily tablet (Duavive®) was recently approved in the European Union for treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (≥12 months since last menses) for whom treatment with progestin-containing therapy is not appropriate [12]. CE 0.45 mg/BZA 20 mg is also approved in the United States (Duavee®) for treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause and prevention of postmenopausal osteoporosis [13]. Safety and efficacy of CE/BZA are supported by 5 double-blind, randomized, placebo- and active-controlled, phase 3 Selective estrogens, Menopause, And Response to Therapy (SMART) trials (Table 1) [14–20]. In SMART-2, CE 0.45 mg/BZA 20 mg significantly reduced the mean daily number of moderate to severe hot flushes by 74% at week 12, and significantly reduced hot flush severity during weeks 3 through 12 ($p < 0.001$ vs placebo) [15]. In SMART-3, CE 0.45 mg/BZA 20 mg significantly increased superficial cells, decreased parabasal cells, and reduced vaginal dryness compared with placebo in postmenopausal women with moderate to severe symptoms of vulvar-vaginal atrophy (VVA) at baseline; however, the most bothersome VVA symptom and vaginal pH were not statistically significantly affected versus placebo [16]. In the 1-year SMART-5 study, CE 0.45 mg/BZA 20 mg showed an increase of 0.24% from baseline in lumbar spine BMD at month 12 compared with a decrease of 1.28% for placebo—a significant ($p < 0.01$) difference of +1.52% [18]. CE/BZA also exhibited beneficial effects on sleep parameters and menopause-related quality of life [18,20,21].

3. Safety and tolerability concerns and contraindications

CE/BZA was well tolerated in the SMART trials; rates of discontinuation due to adverse events were low and similar to placebo (Fig. 1 [SMART-5]) [15–19]. Higher breast density has been shown to be associated with lower mammographic sensitivity (i.e., ability to detect cancer at screening) [22]. In the SMART-5 study, mean mammographic breast density decreased to a comparable extent from baseline to 1 year with CE/BZA (−0.38%) and placebo (−0.44%) while HT (CE/MPA) significantly ($p < 0.001$) increased breast density (+1.60%) from baseline compared with placebo [23]. Similar reductions in breast density were reported for CE/BZA and placebo at 2 years in an ancillary study to SMART-1 [24]. Incidence of breast cancer was low and similar to placebo during up to 2 years of use in the SMART trials [23,24]. The incidence of breast pain/tenderness among women treated with CE/BZA was similar to placebo across SMART trials [15–19] and significantly lower than with CE/MPA in SMART-4 and SMART-5 [17,18].

The addition of BZA to CE reduces the risk of endometrial hyperplasia that can occur with estrogen-only use [12]. Through 12- and 24-month follow-up in the SMART trials, there was no increased risk of endometrial hyperplasia with CE 0.45 mg/BZA 20 mg [14,18]. Incidences of uterine bleeding and spotting were low and similar to placebo [17,18,25]. In SMART-4 and SMART-5, CE 0.45 mg/BZA 20 mg was associated with a significantly higher rate of amenorrhea (Fig. 2 [SMART-5]) and lower incidence of bleeding compared with CE/MPA [17,18]. In one study, amenorrhea was reported in 97% of the women who received CE 0.45 mg/BZA 20 mg during months 10 to 12 [12]. As with other HT, abnormal bleeding requires diagnosis before initiating CE/BZA, and any persistent/recurrent bleeding during treatment warrants investigation to rule out malignancy.

Although CE and BZA individually have been linked to increased venous thromboembolism (VTE) risk [26,27], there appears to be no added risk of combining the two. Across all the phase 3 studies, VTE was a rare event, affecting less than 1 person per 1000 patients [12]. There were few VTEs in the SMART studies (CE 0.45 mg/BZA 20 mg: $n = 3$; placebo: $n = 1$; all deep vein thromboses) [15–19,28]. Although the rates of myocardial infarction with CE/BZA were similar to placebo in the SMART trials, effects of CE/BZA (Fig. 2) on the cardiovascular system require further data collection and analysis. In nonhuman primates (postmenopausal monkeys) fed a high-fat, high-cholesterol diet, CE modestly reduced the severity of atherosclerosis and complicated plaques in the common carotid artery; the addition of BZA did not significantly attenuate these benefits [29]. Statistical power to evaluate VTE and cardiovascular risks is limited by the small number of such events and lack of long-term follow-up data from the SMART trials. If prolonged immobilization is anticipated following elective surgery, CE/BZA should be stopped temporarily beginning 4 to 6 weeks before surgery [12]. Treatment should not be restarted until the woman is completely mobilized [12].

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