Maturitas 76 (2013) 213–220

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Tissue-selective estrogen complexes for postmenopausal women

Sebastian Mirkin, Barry S. Komm*

Pfizer Inc, 500 Arcola Road, Collegeville, PA 19426, USA

ARTICLE INFO

Article history:
Received 22 April 2013
Received in revised form 31 May 2013
Accepted 1 June 2013

Keywords:
TSECs
SERMs
Bazedoxifene
Vasomotor symptoms
Vulvar/vaginal atrophy
Osteoporosis

ABSTRACT

Although hormone therapy using estrogens plus progestogens (EPT) is effective for the management of menopausal symptoms (e.g., vasomotor symptoms and vulvar/vaginal atrophy) and prevention/treatment of postmenopausal osteoporosis, EPT is associated with safety and tolerability concerns. A new alternative to EPT is the tissue selective estrogen complex (TSEC), which partners a selective estrogen receptor modulator (SERM) with one or more estrogens and is designed to treat menopausal symptoms and prevent postmenopausal osteoporosis without the tolerability concerns associated with EPT. The first TSEC to reach advanced clinical development is a combination of the SERM bazedoxifene (BZA) with conjugated estrogens (CE). BZA has been shown to inhibit the stimulatory activity of CE on uterine tissue and breast in vitro and in vivo. In clinical studies, BZA/CE treatment has been associated with significant improvements in menopausal symptoms including hot flushes and vulvar/vaginal atrophy and significant increases in bone mineral density, coupled with reductions in bone turnover marker levels and improvements in sleep and health-related quality of life. Additionally, BZA/CE has been shown to have a neutral effect on endometrial and breast tissue because BZA inhibits the stimulatory effects of estrogens in tissue-selective fashion in these 2 organs. Taken together, results of these preclinical and clinical studies indicate that the benefits of estrogens for treating menopausal symptoms are maintained with BZA/CE without endometrial or breast stimulation, resulting in a safe and effective treatment for symptomatic postmenopausal women.

Contents

Abbreviations: BMD, bone mineral density; BZA, bazedoxifene; CE, conjugated estrogens; EPT, estrogen-progestin therapy; ER, estrogen receptor; LAS, lasofoxifene; LDL-C, low-density lipoprotein cholesterol; MCF-7, Michigan Cancer Foundation-7; MENQOL, Menopause-Specific Quality of Life; MS-TSQ, Menopause Symptoms Treatment Satisfaction Questionnaire; RLX, raloxifene; SERM, selective estrogen receptor modulator; SMART, Selective estrogens, Menopause, And Response to Therapy; TSEC, tissue selective estrogen complex; VMS, vasomotor symptoms; VTE, venous thromboembolic event; VVA, vulvar/vaginal atrophy.

* Corresponding author at: Women's Health, Medical Affairs, Pfizer Inc, 500 Arcola Road, B4204, Collegeville, PA 19426, USA. Tel.: +1 484 865 2776; fax: +1 484 865 4321.
E-mail addresses: Sebastian.Mirkin@pfizer.com (S. Mirkin), Barry.Komm@pfizer.com (B.S. Komm).

0378-5122/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.maturitas.2013.06.003

1. Introduction

In women with an intact uterus, menopausal symptoms are typically treated with estrogen-progestin therapy (EPT) to avoid the endometrial stimulation associated with unopposed estrogen therapy (ET) [1,2]; however, EPT is associated with safety and tolerability issues, including breast stimulation, breast tenderness, and irregular vaginal bleeding [3]. The tissue selective estrogen complex (TSEC), which partners a selective estrogen receptor modulator (SERM) with one or more estrogens, represents a new approach to menopausal therapy designed to improve tolerability [4]. SERMs, such as raloxifene (RLX), lasofoxifene (LAS), and bazedoxifene (BZA), are compounds that exhibit tissue-selective estrogen receptor (ER) agonist and antagonist activities [5]. An optimal TSEC would combine the desired ER agonist activities of estrogens (on vasomotor symptoms [VMS], vulvar/vaginal atrophy [VVA], and bone) with the tissue selectivity of a SERM (specific ER neutral or antagonist activity in endometrium and breast) [4].

BZA paired with conjugated estrogens (CE) is a TSEC in advanced clinical development for the treatment of menopausal symptoms and prevention of postmenopausal osteoporosis [6]. BZA alone has been shown to prevent postmenopausal osteoporosis [7] and reduce fracture risk in postmenopausal women with osteoporosis [8]. In addition, preclinical studies have shown a potent antagonistic effect of BZA in uterine tissue [9,10] and BZA has been associated with favorable endometrial safety, a property that distinguishes it from other SERMs (Fig. 1) [11–14].

Conjugated estrogens is a combination of estrogens, consisting of estrone and equilin, as well as other estrogen compounds (e.g., 17β-dihydroequilin, Δ8,9-dehydroestrone, 17β-estradiol, etc.) [15], each of which is associated with distinct tissue-selective activities [15,16]. The mixture of estrogens within CE, along with the tissue-selective agonist and antagonist activities of BZA, may help to balance estrogenic activities in breast and endometrial tissues, yielding a safe and effective treatment option for postmenopausal women [15,16]. Key preclinical and clinical efficacy and safety findings for BZA/CE will be summarized in this review.

2. Preclinical development of BZA/CE

The efficacy and safety of BZA/CE for menopausal symptom management and osteoporosis prevention have been evaluated in preclinical models [9,17–19]. Preclinical safety evaluations of BZA were conducted in 2 key tissues, the endometrium and breast (Tables 1 and 2). In Michigan Cancer Foundation-7 (MCF-7) breast cancer cells, BZA blocked CE-induced antiapoptotic effects, cell proliferation and growth, and protein and gene expression [20]. In a separate study in MCF-7 cells, BZA/CE was shown to induce unique transcriptional activity among different genes, demonstrating differential activity of BZA/CE in different tissue types [21]. BZA has been shown to inhibit the stimulatory activity of CE on breast tissue in mouse and non-human primate models [18,19,22]. In 2 separate studies [18,19], BZA 2 mg/kg was shown to completely antagonize the stimulatory effects of CE 3 mg/kg on the mammary gland of ovariectomized mice. In ovariectomized mice, comparable doses of BZA were more effective than RLX and LAS at reducing ductal branching and mammary gland amphiregulin stimulation [18]. In ovariectomized cynomolgus macaques [22], increases in epithelial density, lobular enlargement, and ductal proliferation were significantly lower following 6 months of daily BZA 20 mg/CE 0.45 mg compared with CE 0.45 mg alone (all $P < 0.05$), indicating that BZA 20 mg antagonized CE-induced stimulation of breast tissue. In that study [22], the physiological responses were accompanied by a decrease in ERα protein expression and a reduction in markers of ERα activity. The reduced ERα protein expression was believed to be the result of posttranslational degradation because ERα protein levels have been shown to decline with BZA [23], while ERα mRNA levels were unaffected (Fig. 2) [22].

BZA has been shown to function as an antagonist by reducing uterine stimulation induced by unopposed CE in rodents and primates (Table 2) [9,10,18,24,25]. In ovariectomized rats, BZA, but not RLX or LAS, antagonized CE-induced increases in uterine wet weight [18]. In a separate study in ovariectomized mitosis-luciferase mice (a transgenic mouse in which luciferase expression is linked to cell proliferation), pairing BZA 10 mg/kg with CE 3 mg/kg resulted in complete inhibition of the proliferative effects of CE in the uterus [24]. These results were supported by findings in ovariectomized cynomolgus monkeys in which daily doses of BZA 20 mg/CE 0.45 and 0.625 mg resulted in rates of endometrial hyperplasia that were comparable to controls [10]. Treatment with BZA/CE also reduced endometrial proliferation and decreased markers of ERα activity, suggesting that BZA may not only block estrogen binding, but may also increase ERα turnover [10]. Taken together, the antagonistic effects of BZA on the endometrium distinguish it from other SERMs (Fig. 1).

The efficacy of BZA/CE for controlling VMS was evaluated in ovariectomized rats using changes in tail skin temperature as a surrogate endpoint for hot flushes or vasomotor instability [9]. A significant reduction in tail skin temperature was observed with CE 10 mg/kg alone and was maintained when BZA (0.3, 3.0, or 10.0 mg/kg) was combined with CE 10 mg/kg (all $P < 0.05$ vs vehicle control) [9].

Rat osteopenia models were used to evaluate the effects of BZA/CE on bone mineral density (BMD) [9,17]. Treatment with BZA 3.0 mg/kg combined with CE (0.5–5.0 mg/kg) over 6 weeks was shown to preserve BMD in ovariectomized rats, with significant increases in total BMD compared with vehicle control for all dose combinations (all $P < 0.01$) [9]. When all doses of BZA (0.1–1.0 mg/kg) were paired with CE 2.5 mg/kg, BMD increased significantly compared with control (all $P \leq 0.05$) [17]. BZA/CE was also shown to preserve bone microstructure and quality [17].

Overall, preclinical studies demonstrated a favorable efficacy and safety profile for BZA/CE that is distinct from estrogens, SERMs, and other SERM/estrogen combinations (TSECs).

3. Clinical development of BZA/CE

In a series of randomized, double-blind, placebo- and active-controlled phase 3 studies, known as the Selective estrogens, Menopause, And Response to Therapy (SMART) trials, BZA/CE has demonstrated efficacy in managing menopausal symptoms and preventing postmenopausal osteoporosis and has shown a favorable safety and tolerability profile [26–35]. The enrollment criteria, study design, and key findings for each of these studies (except SMART-4 [30] and the recently completed SMART-5) are summarized in Table 3. The results of the 1-year SMART-4 study ($N = 1061$) [30] are not discussed in detail in this review because a different formulation of BZA/CE was evaluated. Regardless, results of the SMART-4 study [30] were similar to those of the SMART-1 study [28,31]; BZA 20 mg/CE 0.45 and 0.625 mg significantly increased lumbar spine and total hip BMD compared with placebo ($P \leq 0.001$), while maintaining endometrial safety [30].

3.1. Effects of BZA/CE on VMS

BZA 20 mg/CE 0.45 and 0.625 mg have been shown to improve VMS in postmenopausal women in the SMART-1 and SMART-2 studies (Table 4) [29,32]. Because VMS may affect 60–85% of postmenopausal women [36,37] and reduction of VMS is one of the key factors used in making treatment decisions, the positive effects of