Review Article
Volume 5:4, 2021

Journal of Clinical Research

ISSN: 2795-6172 Open Access

TSEC (Tissue Selective Estrogens Complex) for Women with Postmenopausal Symptoms

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Abstract

The hormonal changes associated with menopause accounts for an unpleasant menopause symptom and a rapid decrease in bone mineral density. The former significantly impairs women's quality of life, and the latter causes locomotor disorders as well as osteoporosis in old age. Estrogen-Progestin Therapy (EPT) is useful for reducing menopausal symptoms (vasomotor symptoms (VMS) and vulvar/vaginal atrophy (VVA)) in postmenopausal women, and for preventing osteoporosis. However, EPT has the concerns about adverse effects on the breast, and endometrium such as Abnormal Uterine Bleeding (AUB). The Tissue Selective Estrogen Complex (TSEC) has improved safety and tolerability by combining the Selective Estrogen Receptor Modulators (SERMs), which have an estrogen agonist/antagonist effect on tissue selectivity, with estrogen. Bazedoxifene (BAZ), which has the strongest antagonistic effect on the breast and endometrium as SERM, was used in combination with the Conjugated Estrogen (CE). BAZ with CE has the effect of improving VMS and VVA, which is not found in a bazedoxifene monotherapy, and has prevented osteoporosis by normalizing bone metabolism. In addition, BAZ with CE it is safer for the endometrium and breast compared to EPT. It can be an option as a postmenopausal symptomatic Hormone Therapy (HT). In today's world of extended life expectancy, it is obviously meaningful for the old-aged women with postmenopausal symptoms to alleviate the necessity of the treatment for osteoporosis.

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

Introduction

Rationale for TSEC development

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]; With regard to safety and tolerability, EPT may cause breast stimulation, breast tenderness, and irregular vaginal bleeding [3]. The Women's Health Initiative (WHI) conducted a randomized controlled trial or 16,608 postmenopausal patients that demonstrated significant reduction in the rate of fractures with EPT; however, this data also presented an increase in the risk of cardiovascular events, stroke, venous thromboembolism (VTE), and invasive breast cancer associated with the EPT groups [4]. Due to the overall health risks exceeding benefits, hormonal replacement therapy is no longer recommended as the first line for the treatment and prevention of osteoporosis in post and premenopausal women [5].

As the component of EPT, the progestin (medroxyprogesterone acetate; MPA) provides the necessary protection against endometrial hyperplasia [6,7]. However, the WHI studies found an increased risk of invasive breast cancer and breast cancer-related mortality in EPT users, in contrast to a protective effect against breast cancer among hysterectomized women using Conjugated Estrogens (CE) alone [8,9]. Thus, progestin-free alternatives to Hormone Therapy (HT) that provide the relief of menopausal symptoms and the prevention of postmenopausal bone loss would be needed.

Tissue Selective Estrogens Complex (TSEC) is an innovative attempt to combine supplemented estrogens with a Selective Estrogen Receptor Modulators (SERMs) that act as antagonists on several tissues. It is an ideal treatment that eliminates the adverse effects of EPT. SERMs acts as an estrogen agonist in some tissues and as an antagonist in others, such as breast, which have been developed as therapeutic agents for breast cancer [10,11]. SERMs consistently show neutral or protective anti-estrogen activity in the breast and, to varying degrees, show estrogenic effects on bone [12-27] (Figure 1). On the other hand, the effects of SERMs on the endometrium are different. In the endometrium, tamoxifen and lasofoxyfen affect adverse estrogen stimulation, raloxifene has a neutral effect, BZA is neutral, and at high doses it is probably even antagonistic [27-30].

Clinical studies of BZA have shown that it does not irritate the breast or endometrium and provides a beneficial inhibitory effect on bone (equal to or nearly equivalent to raloxifene), clinical development for the prevention and treatment of osteoporosis [24, 29-35]. However, like other SERMs (tamoxifen, raloxifene, lasofoxyfen [19, 27], etc.), BZA can increase or exacerbate the hot flashes [33-35]. Therefore, SERMs alone cannot be used as an alternative to HTs for managing menopausal VMS (vasomotor symptoms). BZA does not irritate the breast or endometrium, making it suitable for studies in combination with estrogen. BZA has been shown to downregulate Estrogen Receptor (ER) protein expression by degrading the receptors in the breast and endometrium. This is the unique effect that distinguishes BZAs from most other SERMs [31,36-40] suggesting that BZA is a so-called pure selective ER down-regulator; at least in the breast and endometrium [3,36].

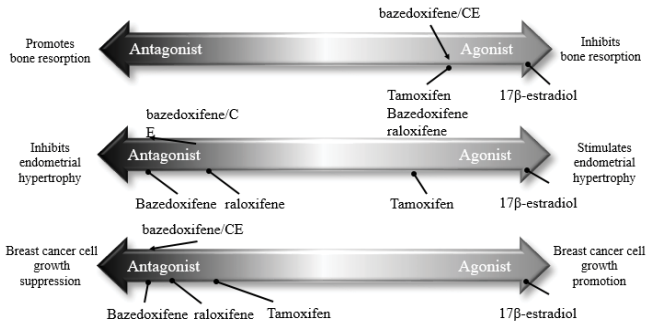

Figure 1. Continuum of tissue selectivity (agonist/antagonist) of SERMs and TSECs, based on *in vivo* studies.

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Received: 19 July 2021; **Accepted:** 02 August 2021; **Published:** 09 August 2021

Literature Review

Clinical efficacy of TSEC

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 (bazedoxifen/Conjugated Estrogens) demonstrated the efficacy in managing menopausal symptoms and preventing postmenopausal osteoporosis and showed a favorable safety and tolerability profile [41-50]. The superiority of TSEC over BZA monotherapy and EPT (CE/MPA) was indicated [51] (Table 1).

Menopausal symptoms: The effects of TSEC (BZA 20 mg/CE 0.45 and 0.625 mg) on menopausal symptoms were examined for VMA (Vasomotor symptoms), VVA (vulvar/vaginal atrophy), Quality of life, sleep, sexual function, and satisfaction with treatment measures [52,53] (Table 2). In the SMART-1 study [44], VMA was improved significant daily moderate to severe from baseline at 4 and 12 weeks of treatment with BZA 20 m/CE 0.45 or 0.625 mg compared to placebo. The frequency of hot flushes was observed (all P<0.05) [44]. Treatment with both doses of BZA/CE was also associated with a significant reduction in mean hot flash severity per day from baseline to 12 weeks compared to placebo (both P<0.001) [44]. These improvements appear to have been maintained for two years [44] and are comparable to those shown in the EPT [1]. TSEC led significant increase in superficial vaginal epithelial cells with BZA 20 mg/CE0.625 mg (P<0.01 vs. placebo), and significant decrease in parabasal cells at 2 years with both doses in SMART-1 study (both P<0.001 vs. placebo) [44]. VVA symptom was improved significant at Week 12 with BZA 20 mg/CE0.625 mg in SMART-3 study (P<0.05 vs. placebo) [42]. In SMART1 and 3 study, the improvements in VMS and VVA with BZA/CE have resulted in those in sleep, quality of life, and satisfaction with treatment [42,48,49,54-56]. In the SMART-1 study, significant improvements from baseline were observed in mean quality of sleep scores after 13 weeks of BZA 20 mg/CE 0.45 and 0.625 mg compared with placebo (both P<0.01); treatment with both doses of BZA/CE was also associated with significant reductions from baseline in time to fall asleep and significant increases in time slept compared with placebo (all P<0.05) [55].

Effects on bone health: A rapid decrease in bone mineral content after menopause causes osteoporosis. Osteoporosis in old age causes lumbar fractures and hip fractures. Postmenopausal osteoporosis comprises a major risk factor for fracture, which leads to considerable morbidity, mortality and economic costs [57,58]. Hip fractures are the second most common cause of hospitalization of elderly patients, with an estimated annual cost of over $650 million [59,60]. The FDA (Food and Drug Administration) approved indications for Prevention of postmenopausal osteoporosis (PMO) are Bisphosphonates (Alendronate and Risedronate, Ibandronate), and SERMs (Raloxifene (RLX)) and TSEC (Conjugated estrogens/bazedoxifene), and Zoledronic acid [61]. The most frequently used bone resorption inhibitors are of concern for atypical fractures caused by excessive bone density [62] and adverse events such as a bone resorption inhibitor-related jaw bone necrosis (ARONJ) [63].

Target	BZA	Estrogens	TSEC
Uterine endometrium	0	-	0
VMS	-	+	+
VVA	-	+	+
Bone	+	+	+
Breast	+	-	0

Abbreviations: +: Positive Response; -: Not Acceptable Response; 0: Neutral Effect; BZA: Bazedoxifen; TSEC: Tissue Selective Estrogens Complex.; VMS: Vasomotor Symptoms; VVA: Vulvar Vaginal Atrophy

Table 1. Targeted responses to various menopausal agents.

Raloxifene and TSEC affects on the mechanisms of action that prevent bone loss by normalizing bone turnover [43,64]. This mechanism is different from that of action of bone resorption inhibitors that suppress only osteoclasts. Also, treatment with SERMs and TSECs does not have the adverse events of ARONJ and atypical fractures, and results in bone formation and bone quality under normal bone turnover [5]. The increases in Bone Mineral Density (BMD) and reductions in bone turnover markers with BZA/CE may contribute to reduce the risk of osteoporotic fractures.

Indeed, bazedoxifene 20 mg monotherapy could reduce the risk of vertebral fracture by 42% (Hazard Ratio [HR], 0.58; 95% CI, 0.38-0.89) [35,43,65-69]. In the SMART-1 study of BZA/CE, BZA 20 mg/CE 0.45 and 0.625 mg significant increased in mean lumbar spine BMD (P<0.001) and total hip BMD (P<0.05) at 12 and 24 months [28]. At Month 24, the increases in BMD were generally greater for women treated with BZA/CE than with RLX [28]. In women who were ≤ 5 years postmenopausal, BZA/CE showed the obvious decreases in serum levels of osteocalcin and C-telopeptide at 24 months with both doses of BZA/CE compared with placebo (all P<0.001) [44] Due to a lack of data on bone fracture, the actual efficacy of BZA/CE for Postmenopausal osteoporosis (PMO) remains unclear. However, the significant reductions were found in serum BTMs with all conjugated estrogens/bazedoxifene doses compared to placebo (P<0.001) [35,43,66-69].

Lipid metabolism on TSEC: TSEC can adversely affect metabolic profile during the menopausal transition, including increased total cholesterol, triglycerides, Low-Density Lipoprotein (LDL) cholesterol, increased lipoprotein (a), and decreased High-Density Lipoprotein (HDL) cholesterol. The effect of BZA/CE on lipid parameters was also evaluated in the SMART-1 study. At 24 months, BZA 20 mg/CE 0.45 and 0.625 mg were total cholesterol (P<0.05 for BZA 20 mg/CE 0.45 mg placebo) and LDL cholesterol (P<0.01 for both placebo) was associated with a decrease from baseline. HDL cholesterol, like triglyceride (P<0.01), HDL-2 cholesterol (P<0.001), and apolipoprotein A1 (P<0.001), is baseline at BZA 20 mg/CE 0.45 and 0.625 mg (P<. Increased from 0.01 vs. placebo) [70]. This TSEC treatment also showed a significant reduction in apolipoprotein B (P<0.05) and lipoprotein (a) (P<0.01) [24]. Both BZA/CE doses were associated with a significant reduction in LDL cholesterol (P<0.01) at week 12 of the SMART-3 trial. BZA 20 mg/CE 0.625 mg showed a slight increase in triglyceride levels that was significant compared to placebo (P<0.05) [71].

Menoposal symptoms	Clinical efficacy	Study
VMS	Significant decreases in the mean daily number of moderate-to-severe hot flushes Significant improvements in treatment satisfaction and vasomotor function	SMART1.SMART2. SMART3 [45,48,50]
VVA	Significant increases in vaginal epithelial superficial and intermediate cells and significant decreases in parabasal cells Significant decrease in vaginal pH Significant improvement in most bothersome VVA symptom	SMART1.SMART3 [43]
Sleep parameters	Significant improvements in sleep parameters (including time to fall asleep, sleep disturbance, sleep adequacy)	SMART1-2 [49,53]
QOL	Significant improvements in treatment satisfaction and quality of life	SMART2-3[49]

Table 2. Clinical efficacy of TSEC.

Discussion

Clinical safety of TSEC

Endometrial safety: At both doses of In SMART-1, CE0.45 mg/BA20 mg and CE0.625 mg/BA20 mg, endometrial hyperplasia was <1 [47,72]. The SMART-1 study confirmed that a minimum of BZA 20 mg was required to protect the endometrium. In the SMART-1 trial, endometrial safety was assessed by the incidence of endometrial hyperplasia, a surrogate marker for endometrial cancer. In the SMART-1 study, endometrial biopsy showed one case (0.32%) of endometrial hyperplasia. There have been no cases of using BZA 20 mg/CE 0.625 mg and BZA 20 mg/CE 0.45 mg or BZA 40 mg/CE 0.45 or 0.625 mg in one year. These hyperplasia rates were not significantly different from placebo. At BZA 10 mg/CE 0.45 and 0.625 mg, endometrial hyperplasia was 3 (0.94%) and 13 (3.81%), respectively. The adjusted mean increases from baseline in endometrial thickness were small (<1 mm) and similar to placebo. The cumulative rate of amenorrhea (absence of bleeding or spotting) with BZA 20 mg/CE 0.45 and 0.625 mg was high (>83%) and similar to placebo; these high rates were sustained over 2 years of treatment [46,73].

Breast safety: HRT with CE 0.625 mg/MPA increases breast cancer risk by about 1.26 times in 5 years. TSEC was expected to have a protective effect on the mammary gland by adding BZA, which is an antagonist to the mammary gland close to the Fulvestrant. The antagonistic effect of BZA on mammary gland cells is stronger than that of raloxifene. In a supplementary retrospective study of the SMART-1 trial, the mean rate of change from baseline in mammography breast density at 24 months was comparable to women treated with BZA/CE (BZA 20 mg/CE 0.45 mg). -0.39%; BZA 20 mg/CE 0.625 mg, -0.05%) and placebo-treated patients (-0.42%) [51]. At 24 months, the incidence of intervention for breast or abnormal mammograms were almost same. Similarly, no difference in breast cancer incidence was observed between the BZA/CE and placebo groups over 2 years (BZA 20 mg/CE 0.45 mg, n=1; BZA 20 mg/CE 0.625 mg, n=0; placebo, n=1) [34]. Positive tolerability profiles associated with BZA/CE personnel are in sharp contrast to EPT and are associated with an increased risk of bleeding and breast pain in some women [42,44,47,74-77].

Safety against thrombosis/Coagulation parameters: Changes in coagulation factors have been shown to occur during the menopausal transition, including increased levels of coagulation protein Factor VII and fibrinogen [76]. On the other hand, there is concern that estrogen supplementation by TSEC will increase the risk of thrombosis, so it is important to examine coagulation factors in TSEC. In the SMART-1 trial, the incidence of venous thromboembolism (VTE) was 1.56 per 1000 female years in the placebo group, compared with 0.75 per 1000 female years in the BZA/CE combination therapy group (relative risk, 0.48; 95% confidence interval, 0.05-4.66) [42,44,47]. At 24 months, fibrinogen ($P<0.001$), protein S activity ($P<0.01$), and antithrombin III activity ($P<0.05$ and $P<0.01$ of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg) level has decreased significantly from baseline. Both doses did not affect partial thromboplastin time, prothrombin time, or D-dimer levels compared to placebo. Plasminogen activity was significantly increased from baseline at both doses ($P<0.001$) [44].

Clinical use of TSEC: A combination of conjugated estrogens 0.45 mg with bazedoxifene 20 mg (Duavee, Pfizer) received FDA approval in 2013 for use in postmenopausal women with an intact uterus for the prevention of osteoporosis and for the treatment of moderate-to-severe vasomotor symptoms [77]. However, there are areas where Duavee is not marketed. In several areas, bazedoxifene monotherapy (Viviant, Pfizer) is marketed as an osteoporosis treatment.

Several variations for TSEC treatment are proposed. 1 mg of micronized estradiol, 0.625 mg of conjugated equine estrogen, and 5 μg of ethinylestradiol have been converted to equivalent estrogenic activity [78,79]. TSEC combinations using raloxifene as the SERM were also investigated clinically. Although there were preliminary indications of efficacy in some of the studies using oral or nonoral estrogen/SERM combinations, these TSECs generally provided inadequate endometrial protection [80]. Hence careful evaluation and selection of the doses of the two components was necessary to find the doses that balance endometrial protection with therapeutic effect. Combination of 20 mg of bazedoxifene and 1 mg of micronized estradiol or 0.625 mg of conjugated estrogens can be considered as an option. Since TSEC has a dose-dependent effect, it may be necessary to follow up on the success of TSEC and adjust the dose. As TSEC combines CE or 17 βestradiol with BZA, it is necessary to evaluate the overall effect of multiple estrogen components. It is better to evaluate the effect by a marker that indirectly reflects the effect of estrogen, instead of measuring the amount of each estrogen agent.

Bone metabolism markers are mainly used to reflect the therapeutic effect of osteoporosis. Since estrogen-related preparations such as SERM have an action of normalizing bone turnover, it is necessary to measure bone resorption and bone absorption markers at the same time to verify that bone turnover is improved. Marker combinations include C-terminal telopeptide of type 1 collagen and procollagen type 1 N propeptide, Tartrate-Resistant Acid Phosphatase-5b and Bone Specific Alkaline Phosphatase [63]. In addition, estrogen is not the only rate-determining factor for bone turnover, and other factors such as vitamin D need to be taken into consideration during treatment [81]. In terms of cost efficiency, the EPT Prempro is about $200 and the Duavee is about $200 [61].

Conclusion

The TSEC is a new approach effects of estrogens on menopausal symptoms or bone loss with the protective effects of SERMs on the breast and endometrium. It is also expected to improve lipid metabolism and coagulation parameters and will be a future option as HT for the menopausal women. Compared to EPT, the cost of treatment is almost equal. In addition, the advantage of TSEC is that there is less abnormal uterine bleeding and breast tenderness. The TSEC seems to be a suitable method of treatment for symptomatic women in their late 40s to 50s who have just reached menopause and have strong VMS.

It is necessary for TSEC to investigate the clinical effect on bone and the safety on the endometrium and breast on a larger scale in the long term. Further improvements for the types of estrogen and the route of administration for drugs would be required.

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How to cite this article: Ota, Ikuko, Yoshiaki Ota and Fuminori Taniguchi. "TSEC (Tissue Selective Estrogens Complex) for Women with Postmenopausal Symptoms". *J Clin Res* 5 (2021): 135.