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Review Article

An Overview of the Clinical Efficacy and Safety of Tissue Selective Estrogen Complex: From the Selective Estrogens, Menopause, and Response to Therapy (SMART) Trials

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Hormone therapy (HT) is the most effective treatment for menopausal symptoms, and reduces both spinal and non-spinal postmenopausal osteoporotic fractures. However, a Women's Health Initiative (WHI) trial revealed that progestin-containing HT is associated with higher incidences of breast cancer and coronary heart disease than those associated with placebo. Tissue selective estrogen complex (TSEC) is a novel progestin-free HT option composed of conjugated estrogens (CE) and a selective estrogen receptor modulator. CE at a dose of 0.45 ㎎ combined with 20 ㎎ of bazedoxifene was the first TSEC medication approved in the United States and Korea for women with moderate to severe menopause-related vasomotor symptoms (VMS) and for preventing postmenopausal osteoporosis. This review summarizes the clinical efficacy, safety, and tolerability of TSEC as obtained from the five SMART clinical trials.

Key Words: Efficacy, Hormone therapy, Safety, Tissue selective estrogen complex

Hormone therapy (HT) is the most effective treatment for menopause-related VMS.[1-4] It also prevents postmenopausal osteoporotic fractures including spinal and non-spinal fractures. HT is approved by the U.S. Food and Drug Administration (FDA) for the prevention of osteoporosis and for relief from VMS and vulvovaginal atrophy (VVA) associated with menopause.[2,5] In women with an intact uterus who show perimenopausal symptoms, estrogen-progestogen therapy (EPT) is recommended because systemic estrogen-only therapy (ET) is associated with an increased risk of endometrial cancer, hyperplasia, and irregular bleeding.[1,2,6,7] EPT is effective in the management of climacteric symptoms; however, it is associated with safety and tolerability concerns.[8] Randomized controlled trials by the WHI have revealed that EPT is associated with a high incidence of breast cancer and mortality.[3,9] On the contrary, a lower incidence of breast cancer was observed in postmenopausal women who had undergone hysterectomy and were using ET (hazard ratio [HR], 0.77; 95% confidential interval [CI], 0.62-0.95).[10] Additionally, the incidence of coronary heart dis-

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ease (CHD) significantly increased by 29% in women taking EPT compared to that in women in the placebo group.[3] However, the use of systemic ET did not increase the incidence of CHD in postmenopausal women who had undergone hysterectomy (HR, 0.91, 95% CI, 0.75-1.12).[11] Therefore, there has been a need for progestin-free treatment options with clinically proven efficacies and good safety profiles, which can protect the endometrium from negative estrogenic effects.[12]

TSEC combines a selective estrogen receptor modulator (SERM) with one or more CE. TESC is a new approach to treating menopausal symptoms and postmenopausal osteoporosis, and is an alternative to EPT, that can be used to treat women with an intact uterus.[8,13] SERMs are compounds that act as estrogen receptor (ER) agonists in some tissues and as antagonists in others. Different SERMs provide different tissue-specific actions with varying levels of agonist and antagonist activities.[2,13] Bazedoxifene (BZA) is a third-generation SERM that is approved for the prevention and treatment of osteoporosis in Europe (Conbriza®) and Korea (Viviant®). BZA has shown favorable preclinical effects on the skeleton, in VMS, and on lipid profiles. BZA also helps to maintain mammary and uterine safety.[12,14] The rationale for selecting BZA as the SERM in TSEC is that BZA can offset the estrogenic stimulation of endometrial and breast tissues without the need for progestin. This is particularly useful for menopausal women with an intact uterus, without aggravating VMS.[15] Several preclinical studies have demonstrated that BZA effectively negates the adverse estrogenic effects of CE on the endometrium and the breast.[16-20] SMART trials, which consist of five randomized, double-blind, placebo- and active-controlled phase 3 trials, were conducted to evaluate the efficacy and safety/tolerability of CE/BZA in postmenopausal women with a uterus (Table 1). From these trials, CE 0.45 ㎎/BZA 20 ㎎ became the first TSEC to be approved in the United States (Duavee®), the Europe Union, and Korea (Duavive®).[12]

This review summarizes the current knowledge of the clinical efficacy, safety, and tolerability of TSEC published from the five SMART trials.

CLINICAL EFFICACY OF BZA/CE IN SMART TRIALS

1. HOT FLUSHES

A total of 3,397 healthy, postmenopausal women aged 40 to 75 years with an intact uterus were enrolled in the SMART-1 trial. Analysis of the SMART-1 trial showed that all the BZA (10, 20, or 40 ㎎)/CE (0.45 or 0.625 ㎎) doses provided significant relief from moderate and severe hot flushes compared to that provided by the placebo at most time points.[21] At week 12, the adjusted mean percentage reduction in the average daily number of hot flushes was 51.7-85.7% from baseline in the BZA/CE treatment group, while that for the placebo- and raloxifene-treatment groups were 17.1% and 44.1% respectively. However, the

Table 1. SMART trial study designs

Study	Duration	Main Endpoints	Treatment Arms	No. of Subjects
SMART-1	24 mo	• Dose ranging • Endometrial hyperplasia at 12 mo • Bone mineral density at 24 mo • Vasomotor symptoms • Vaginal maturation	• BZA 10, 20, 40/CE 0.45 • BZA 10, 20, 40/CE 0.625 • Raloxifene 60 • Placebo	3,397
SMART-2	3 mo	• Vasomotor symptoms	• BZA 20/CE 0.45 • BZA 20/CE 0.625 • Placebo	318
SMART-3	3 mo	• Vulvar/vaginal atrophy	• BZA 20/CE 0.45 • BZA 20/CE 0.625 • BZA 20 • Placebo	652
SMART-4	12 mo + 12 mo extension	• Supportive safety study • Endometrial hyperplasia • Bone mineral density	• BZA 20/CE 0.45 • BZA 20/CE 0.625 • CE 0.45/MPA 1.5 • Placebo	1,061
SMART-5	12 mo	• Endometrial hyperplasia • Bone mineral density • Breast density • Sleep/quality of life (substudy)	• BZA 20/CE 0.45 • BZA 20/CE 0.625 • CE 0.45/MPA 1.5 • BZA 20 • Placebo	1,843

decrease in the daily number of hot flushes reported with BZA (40 ㎎)/CE (0.45 or 0.625 ㎎) was not as significant as that noted with BZA (10 or 20 ㎎)/CE (0.45 or 0.625 ㎎) at most time points.

In the SMART-2 trial, postmenopausal women with moderate to severe hot flushes (≥ 7/day or 50/week) were randomized to BZA 20 ㎎/CE 0.45 ㎎, BZA 20 ㎎/CE 0.625 ㎎, or placebo, once daily for 12 weeks.[22] Compared with the placebo, both doses of CE/BZA resulted in a significant reduction in the number and severity of hot flushes at weeks 4 and 12 ($P < 0.001$) from baseline. Treatment with 20 ㎎/CE 0.45 ㎎ BZA and 20 ㎎/CE 0.625 ㎎ BZA reduced the mean daily number of hot flushes from baseline by 74% and 80%, respectively, at week 12, compared with a 51% reduction for the placebo. In addition, both doses of BZA/CE reduced the mean daily severity score of hot flushes from baseline by 38% and 52%, respectively, at week 12 compared with a 17% reduction for the placebo. A significant reduction in the number and severity of hot flushes was observed during weeks 3 to 12 in both BZA/CE groups compared with those of the placebo.

2. SLEEP AND HEALTH-RELATED QUALITY OF LIFE

According to the National Institutes of Health (NIH) State-of-the-Science Conference statement,[23] women seem to experience more sleep disturbances as they progress through the menopausal stages. The prevalence of sleep disturbance varies from 16 to 42% during premenopause, from 39 to 47% during peri-

menopause, and from 35 to 60% during postmenopause. An analysis of the Study of Women's Health Across the Nation (SWAN) revealed that more frequent VMS in postmenopausal women were associated with greater episodes of sleep difficulty.[24] In the SMART-2 trial, significant improvements from baseline were observed in postmenopausal women receiving BZA/CE treatment at week 12, regarding time taken to fall asleep, sleep adequacy, sleep disturbance, and sleep problem indices Ⅰ and Ⅱ. The Medical Outcomes Study (MOS) sleep scale was used for assessments in the trial.[22] The sleep/health-related quality of life (HRQoL) substudy of the SMART-5 randomized study enrolled 459 women with bothersome moderate to severe VMS who administered BZA 20 ㎎/CE 0.45 ㎎, BZA 20 ㎎/CE 0.625 ㎎, BZA 20 ㎎, CE 0.45 ㎎/medroxyprogesterone acetate (MPA) 1.5 ㎎, or placebo for 1 year.[25] By month 3, improvements in the MOS sleep parameters with BZA/CE and CE/MPA treatments were not significant compared with improvements associated with the placebo. By month 12, however, treatment with BZA/CE and CE/MPA had significantly improved time to fall asleep and sleep disturbance. In addition, both doses of BZA/CE, and CE/MPA significantly improved time to fall asleep and sleep disturbance. Pinkerton et al.[25] noted that BZA/CE had a direct effect on sleep in symptomatic women in the SMART-2 trial, whereas effects of BZA/CE on sleep were indirect in the SMART-5 trial and it was largely mediated via hot flush improvements. The authors suggested that improvements occurred directly in women with moderate to severe VMS, and indirectly in less symptomatic women.

VMS can have a significant negative impact on HRQoL and sleep disturbances, thereby contributing to physical and psychosocial impairments.[26] In the SMART-2 trial, menopause-related HRQoL was assessed by the Menopause-Specific Quality of Life (MENQOL) scale.[22] Participants treated with BZA/CE had significant improvements in individual and total MENQOL scores from baseline. The sleep/HRQoL substudy of the SMART-5 trial revealed that the BZA 20 ㎎/CE 0.625 ㎎ group showed significant improvement in total MENQOL scores compared with those of the placebo at 3 and 12 months, whereas the BZA 20 ㎎/CE 0.45 ㎎ group showed significant improvements at 12 months only.[25]

3. VULVOVAGINAL ATROPHY

In the SMART-1 trial, a dose-related attenuation of the beneficial estrogenic effect on vaginal atrophy with increasing doses of BZA was observed.[21] Treatment with BZA (20 ㎎)/CE (0.45 or 0.625 ㎎) was significantly more effective in increasing the mean proportion of superficial and intermediate cells from baseline at most time points, while the mean proportion of parabasal cells decreased. Additionally, there was a significantly lower incidence of dyspareunia with BZA (20 ㎎)/CE (0.45 or 0.625 ㎎) during weeks 9 to 12. In the SMART-3 randomized trial, a total of 664 postmenopausal women aged 40-65 years

were administered BZA 20 ㎎/CE 0.625 ㎎, BZA 20 ㎎/CE 0.45 ㎎, BZA 20 ㎎, or placebo once daily for 12 weeks.[27] BZA 20 ㎎/CE 0.625 or CE 0.45 ㎎ increased superficial cells and intermediate cells, and decreased parabasal cells compared with the effects of the placebo. Improvements in vaginal dryness were also observed with both BZA/CE doses. In addition, treatment with BZA (20 ㎎)/CE (0.45 or 0.625 ㎎) for 12 weeks was shown to significantly improve sexual function and quality-of-life measures in symptomatic postmenopausal women.[28] However, the most bothersome symptoms and vaginal pH significantly improved with BZA 20 ㎎/CE 0.625 ㎎, but not with BZA 20 ㎎/CE 0.45 ㎎, compared with the effects associated with the placebo. BZA/CE has not been approved by the FDA for the treatment of VVA in postmenopausal women.[29]

4. BONE

The SMART-1 trial included two substudies on osteoporosis: the Osteoporosis Prevention Ⅰ Substudy (substudy Ⅰ), and the Osteoporosis Prevention Ⅱ and Metabolic Substudy (substudy Ⅱ). Substudy Ⅰ examined women at 40 international sites, who were postmenopausal for more than 5 years. On the other hand, substudy Ⅱ involved women enrolled at 25 international sites, who were 1–5 years postmenopausal.[30] All participants were randomly assigned to one of eight treatment groups: BZA (10, 20, or 40 ㎎) with CE (0.45 or 0.625 ㎎), raloxifene (60 ㎎), or placebo. In both substudies, bone mineral density (BMD) at the lumbar spine and total hip increased more significantly at all the BZA/CE doses compared with that achieved with the placebo. However, BMD at the lumbar spine increased more significantly for most BZA/CE doses compared with the effects associated with raloxifene.[30] Improvements in lumbar spine BMD were also significantly greater with all BZA/CE treatments than with the placebo at months 12 and 24. In addition, there was a significant decrease in the bone turnover markers (BTMs), osteocalcin and N-telopeptide. The BTMs decreased with all the doses of BZA/CE compared with those with the placebo, and with most of the BZA/CE doses compared to those of raloxifene.

CE and BZA protect against loss of BMD in postmenopausal women when administered separately.[29] In the SMART-1 trial, higher doses of CE combined with BZA resulted in increases in lumbar spine BMD. However, it was observed that TSEC with higher doses of BZA resulted in decrease in lumbar spine BMD. In the SMART-5 trial, increase in lumbar spine BMD as a result of treatment with CE 0.45 ㎎/MPA 1.5 ㎎ was significantly greater than that for BZA 20 ㎎/CE 0.45 ㎎ at 12 months.[31] CE is a more potent antiresorptive agent than BZA. The authors therefore suggested that attenuation of BMD responses should be expected if BZA is given together with CE, since both drugs bind to the same receptor.[31]

CLINICAL SAFETY AND TOLERABILITY OF CE/BZA IN THE SMART TRIALS

1. ENDOMETRIAL SAFETY

The SMART-1 trial included a 24-month follow-up period. During this period, BZA 20 ㎎ proved to be the least efficacious in the prevention of endometrial hyperplasia, when it was administered together with CE (0.45 or 0.625 ㎎).[32] Over the 24 months, the incidence of endometrial hyperplasia due to BZA (20 or 40 ㎎)/CE (0.45 or 0.62 ㎎) was < 1%, which was within the predefined acceptable limit of ≤ 2%. However, the results were not significantly different from those obtained with the placebo. On the contrary, the incidence rate of endometrial hyperplasia at month 24 was 7.14% with 10 ㎎/CE 0.625 ㎎ BZA and 2.53% with 10 ㎎/CE 0.45 ㎎ BZA.32 Additionally, endometrial thickness with BZA (20 or 40 ㎎)/CE (0.45 or 0.625 ㎎) was not significantly different from that observed in the placebo group. These results suggested that treatment with progestin-free therapy for menopausal symptoms in women with an intact uterus may be a new option. In the SMART-5 trial, subjects received daily oral BZA (20 ㎎)/CE (0.45 or 0.625 ㎎), BZA 20 ㎎, CE 0.45 ㎎/MPA 1.5 ㎎, or placebo. At 12 months, endometrial hyperplasia incidence was less than 1% and this was similar among the groups with low rates of atypia.[31] In addition, the number of proliferative endometrial cases at 12 months was low (< 1%), and also similar among the groups. Women treated with BZA/CE and CE/MPA showed significantly greater increases in endometrial thickness from baseline at 12 months compared to those of the placebo group. The adjusted mean changes in endometrial thickness from baseline were 0.17 ㎜ for BZA 20 ㎎/CE 0.45 ㎎ ($P < 0.05$), 0.51 ㎜ for BZA 20 ㎎/CE 0.625 ㎎ ($P < 0.001$), and 0.78 ㎜ for CE/MPA ($P < 0.001$), as opposed to 0.09 ㎜ for placebo. Endometrial polyps were confirmed by endometrial biopsies. The number of women who developed polyps in the BZA 20 ㎎/CE 0.45 ㎎ and CE/MPA groups was significantly higher than that in the placebo group.[31]

2. CARDIOVASCULAR SAFETY

From 12 to 24 months during follow-up, serious cardiovascular and treatment-emerent adverse events were observed in the women treated with BZA/CE, as compared with those who received the placebo.[21,29,31,33] CE and BZA increase the risk of venous thromboembolism (VTE); however, no added risk of VTE was observed when the two drugs were co-administered in the trials.[12] By the twelfth month during follow-up, there were no reports of VTE associated with BZA 20 ㎎/CE 0.45 or 0.625 ㎎ treatments. There was however one report of superficial phlebitis in the CE 0.45 ㎎ /BZA 20 ㎎ group, and another report of cerebrovascular accident (CVA) in the CE 0.625 ㎎/BZA 20 ㎎ group.[34]

Actually, cardiovascular events such as VTE, CVA, or CHD were rare in this young population of postmenopausal women in the 2-year duration of the SMART studies. Accordingly, statistical power to evaluate VTE and cardiovascular risks was limited by the small number of such events and short follow-up period in the SMART trials.[12]

Komm et al.[35] conducted a meta-analysis of the five SMART trials for further evaluation of the cardiovascular safety of CE/BZA to enhance the statistical power of the data. In women taking CE 0.45 ㎎/BZA 20 ㎎, the rate of VTE, stroke, and CHD per 1000 women-years (95% confidence interval, CI) was 0.3 (0.0–2.0), 0.4 (0.0–2.4), and 2.6 (0.0–5.6) respectively. Compared with placebo, the relative risk (95% CI) with any CE/BZA dose was 0.5 (0.1–1.8) for VTE, 0.5 (0.1–2.6) for stroke, and 0.63 (0.23–1.74) for CHD. The results suggested that CE 0.45 ㎎/BZA 20 ㎎ and CE 0.625 ㎎/BZA 20 ㎎ demonstrated a better cardiovascular safety profile for up to 2 years compared with that of the placebo, in generally healthy postmenopausal women. Changes in body weight in all the CE/BZA groups were small and not statistically different from those observed in the placebo group.[35]

3. BREAST SAFETY AND TOLERABILITY

An ancillary retrospective study in a subset of non-hysterectomized postmenopausal women enrolled in the SMART-1 trial showed that treatment with BZA 20 ㎎/CE 0.45 ㎎ or BZA 20 ㎎/CE 0.625 ㎎ for 24 months did not affect mammographic breast density.[36] In the SMART-5 study, BZA/CE demonstrated non-inferiority compared with that of the placebo for changes in breast density.[37] Mean mammographic breast density over one year decreased from baseline with BZA 20 ㎎/CE (0.45 or 0.625 ㎎) compared with that of the placebo (0.44%). On the other hand, CE 0.45 ㎎/MPA 1.5 ㎎ significantly increased breast density (1.60%) from the baseline compared with the effect associated with the placebo. The incidences of breast cancer were low but were similar among the groups: 2/445 for BZA 20 ㎎/CE 0.45 ㎎, 0/474 for BZA 20 ㎎/CE 0.625 ㎎, 1/220 for CE 0.45 ㎎/MPA 1.5 ㎎, and 1/474 for in the placebo group.[37] The incidence of breast tenderness in the BZA/CE groups was similar to that in the placebo group, but significantly lower than that in the CE/MPA group in the SMART-4 and SMART-5 trials, respectively.[31,33,37]

4. OTHER SAFETY AND TOLERABILITY CONCERNS

Treatment with BZA (20 or 40 ㎎) or with CE (0.45 or 0.625 ㎎) was associated with a lower incidence of bleeding or spotting events compared with that observed with the placebo. The studies also indicated that the cumulative amenorrhea profiles for subjects treated with BZA (20 or 40 ㎎)/CE (0.45 or 0.625 ㎎) were similar to those of subjects in the placebo group.[38] Only treatment with BZA 10 ㎎/CE 0.625 ㎎ was reported to be associated with slightly lower cumulative amenorrhea rates than those associated with the placebo during the first year of the trials. There was also a small but significantly higher incidence of bleeding or spotting events observed in patients who received BZA (10 ㎎)/CE (0.45 or 0.625 ㎎) than in those who received the placebo. In the SMART-5 trial, subjects treated with BZA (20 ㎎)/CE (0.45 or 0.625 ㎎) had cumulative amenorrhea rates similar to those who received the placebo. The cumulative amenorrhea rates were,

however, significantly higher in the BZA (20 ㎎)/CE (0.45 or 0.625 ㎎) group than in the CE 0.45 ㎎/MPA 1.5 ㎎ group.[31] Non-cumulative rates of spotting and bleeding were consistently higher in women treated with CE 0.45 ㎎/MPA 1.5 ㎎ than in women treated with BZA 20 ㎎/CE (0.45 or 0.625 ㎎), those treated with BZA 20 ㎎, or those in the placebo group.

Treatment with BZA/CE showed largely beneficial or no effects on lipids and coagulation markers.[29] Pooled analysis of three SMART trials (SMART-1, -4, and -5) showed that there was a significant improvement in high-density lipoprotein cholesterol (LDL-C). At 12 and 24 months, treatment with BZA/CE had resulted in significant reductions from baseline in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and the LDL-C/HDL-C ratio compared with the effect associated with the placebo.[39] In the SMART-5 trial, BZA 20 ㎎/CE (0.45 or 0.625 ㎎) treatments were associated with small but significant effects on hemostatic variables including reductions in antithrombin, plasminogen activator inhibitor-1, and fibrinogen activity. Treatment with BZA 20 ㎎/CE (0.45 or 0.625 ㎎) also resulted in an increase in plasminogen activity at 12 months, higher than that observed with the placebo treatment.[34]

APPROPRIATE CANDIDATES FOR TSEC THERAPY

BZA/CE is an effective and well-tolerated alternative to EPT for the treatment of moderate to severe VMS and for the prevention of osteoporosis in postmenopausal women with an intact uterus.[2] However, choosing between the two treatments is a very difficult task, since there are few direct comparisons between the efficacies of EPT and TSEC. Palacios et al.[12] have suggested that appropriate candidates for BZA/CE therapy instead of EPT in healthy postmenopausal women suffering from moderate to severe VMS with a intact uterus include:

(1) Women who experience bothersome vaginal bleeding or breast pain/tenderness.

(2) Women who experience other intolerable side effects of progestin-containing therapy including nausea, hirsutism, headache, dizziness, weight gain, and cyclical mild depression. Postmenopausal women with mood symptoms similar to those of premenstrual syndrome or premenstrual dysphoric disorder are also suitable candidates.

(3) Women with decreased glucose tolerance and increased insulin resistance, which are conditions associated with oral progestin-containing therapy.

(4) Women with increased breast density on mammograms, which may impede mammographic detection of breast cancer.

(5) Women who decline progestin-containing HT based on concerns about increased risk of breast cancer due to EPT.

In general, BZA/CE can be considered as an appropriate alternative if progestins are inappropriate or if the benefit-risk profile is more favorable compared with that observed when

treating with progestin-containing HT. Palacios et al.[12] have suggested that women in group (5) should be advised that data on the long-term effects of BZA/CE on the risk of developing breast cancer are not currently available.

CONCLUSION

TSEC is an effective and well-tolerated progestin-free alternative to conventional EPT. It is used for the treatment of moderate to severe VMS in postmenopausal women who have not undergone hysterectomy. TSEC is also used for the prevention of osteoporosis in such women. It has acceptable endometrial, breast, cardiovascular, and overall safety and tolerability profiles. BZA/CE may be the appropriate treatment of choice for symptomatic postmenopausal women who cannot tolerate the side effects of progestin. BZA/CE can also be given to women who decline EPT due to concerns about an increased risk of breast cancer development. However, long-term studies on the safety of BZA/CE treatment, including those on the risks for developing cardiovascular diseases and VTE due to the treatment need to be conducted. In addition, further comparative randomized controlled trials on the differences in efficacies of BZA/CE and EPT treatments are needed, in order to make selection of the more appropriate treatment easier.

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Peer Reviewer's Commentary

Tissue selective estrogen complex (TSEC) is a novel progestin-free HT option composed of conjugated estrogens (CE) and a selective estrogen receptor modulator. It is used for the treatment of moderate to severe VMS in postmenopausal women who have not undergone hysterectomy. This review well summarized the clinical efficacy, safety, and tolerability of TSEC as obtained from the five SMART clinical trials.

(Editorial Board)