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REVIEW ARTICLE

Innovative Treatment in Menopause: Tissue-Selective Estrogen Complex (TSEC)

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Introduction

Menopause is not a disease, therefore it is not always necessary to treat women in the transition and in menopause. However, hormonal changes can be associated with symptoms, the most common are hot flashes and night sweats. Others like dyspareunia, vaginal dryness, mood swings and sexual disfunction can frequently appear. In addition, there is an increase in bone resorption on ocassions leading to osteopenia and osteoporosis. Women who are severely symptomatic, 25-30% more or less of all menopause women, have their quality of life affected [1].

Hormone therapy is the most effective treatment for symptoms. It is the gold standard for relieving vasomotor symptoms (VSM) and also it improves other problems related with menopause. Furthermore, hormone therapy is effective to improve the loss of bone mass. Thus, there is a global consensus statement on hormone therapy that concluded that for symptomatic women the benefits are higher than risks before 60-years-old or within 10 years after menopause [2-4].

The most prescribed therapy for menopause in the USA was a combination of conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) but breast cancer risk was a major safety concern with this regimen. Randomized, controlled trial data from The Women's Health Initiative (WHI) study reported an increase relative risk of breast cancer after 5.2 years of treatment [4]. CEE alone did not increase the risk of breast cancer in the WHI study, and after 7 years of intervention, it reduced breast cancer risk at the 6 years follow-up [5]. In 2016 the same authors wrote a paper explaining maybe there was a mistake in the interpretation of WHI study; they remarked the possible role of the progestogen in increasing the risk of breast cáncer and stimulated the need to develop safer alternatives [6].

Tissue-selective estrogen complex (TSEC) is a innovative, alternative treatment which combines CEE and a selective estrogen receptor modulator, bazedoxifene (BZA) rather than a progestogen for uterine protection. The reason for this combination was to blend the anti-estrogen effects on the uterus and breast of BZA, maintaining the positive estrogenic effects in vasomotor, vaginal symptoms and skeletal bone mass, without the need of progestogen. This combination (CEE/BZA) is the first TSEC approved, by the FDA (US Food and Drug Administration) and EMA (European Medicines Agency) [7,8]. In Europe, it is indicated for the treatment of estrogen deficiency symptoms in postmenopausal women with uterus for whom treatment with progestin-containing therapy is not appropriate. The FDA has approved the combination for women who suffer from

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moderate-to-severe hot flashes associated with menopause and also to prevent osteoporosis after menopause.

The aim of this review was to summarize clinical data on the action and safety of the TSEC. We performed literature searches with PubMed, Scopus and MEDLINE for articles published in English through March 2018 using the following keywords: TSEC, bazedoxifene, conjugated estrogens, HT, menopausal symptoms, quality of life, sexuality, bone metabolism cardiovascular risk, endometrial safety and breast safety. Full articles that met the inclusion criteria were reviewed in detail.

Clinical Trials

Clinical trials designed to assess the activity and safety of the TSEC have been performed on more than 7500 women around the world in a series of double-blind, randomized, placebo-controlled, phase 3 studies named SMART [9-13]. They are summarized in Table 1. Several doses were analyzed, but CEE 0.45mf/ BZA 20 mg is the only approved and marketed for having the best risk-benefit profile.

Vasomotor symptoms

The efficacy of TSEC for the treatment of vasomotor symptoms in menopause were evaluated in SMART-1 and 2 [9,10]. SMART-2 used the number and intensity of hot flashes as its main variable. TSEC significantly decrease the frequency and severity of hot flashes in comparison with placebo. The effect started to be significant at week 4. In SMART 1 the effects remained after 2 years of treatment. An analysis of both clinical trials by years since menopause showed that compared with placebo, TSEC significantly reduced mean daily frequency and severity of hot flashes in women during the first 5 years postmenopause and from 6 years and on. Compared with the effect showed in Cochrane Systematic Review Meta-analysis of hormone therapy with estrogen and progesterone, the clinical benefit of TSEC in SMART trials was very similar [14]. However, there are no data comparing the reduction in hot flashes directly CEE/ BZA and other menopause hormone therapy. Only one study showed a similar efficacy for relieving hot flashes between CEE /BZA and CEE/MPA, but the principal purpose of this article was to study the sleep and health-related quality of life [15].

Sleep

Night hot flashes can induce sleep disturbances. It implies to have daytime impairments in alertness and acuity and can lead to forgetfulness, carelessness, and irritability. In addition to their effects on vasomotor symptoms, TSEC is effective in improving sleep quality. Using a specific sleep scale, improvements were report-

Table 1: Main results from the SMART trials.

Study	Objective	Main results
SMART 1	Effects on menopausal symptoms, metabolic parameters, and safety vs. BZA, CE/MPA, and PBO	- Reduction of the moderate-severe daily hot flushes ($p < 0.05$ vs. PBO) and its severity ($p < 0.001$ vs. PBO) - Improvements in sleep parameters ($p < 0.05$ vs. PBO) - Improvements in lipid parameters and only minor effects on some coagulation parameters - Endometrial, breast safety
SMART 2	Safety and efficacy treating moderate to severe vasomotor symptoms vs. BZA, CE/MPA, and PBO	- Reduction in the number and severity of hot flashes ($p < 0.001$ vs. PBO) - Improvements in sleep parameters ($p < 0.05$ vs. PBO) - Improvements in satisfaction and quality of life ($p < 0.05$ vs. PBO)
SMART 3	Efficacy and safety of two doses of TSEC vs. PBO for the treatment of moderate to severe VVA	- Increase in superficial and intermediate cells, and decrease in parabasal cells ($p < 0.01$ vs. PBO) - Improvements in satisfaction, vasomotor symptoms, sexual function, and quality of life ($p < 0.05$ vs. PBO)
SMART 4	Endometrial safety and BMD effects vs. CE/MPA and PBO	- Endometrial safety similar to PBO. Bleeding and breast tenderness lower than HT ($p < 0.05$) - Improve lumbar spine and total hip BMD ($p < 0.001$ vs. PBO) Favorable safety/tolerability profile over 1 year
SMART 5	Endometrial safety and BMD effects vs. BZA alone, HT, and PBO	- Low endometrial hyperplasia incidence (< 1%) in all groups - Cumulative amenorrhea rates similar to PBO and BZA and higher than HT ($p < 0.001$) - Improve lumbar spine and total hip BMD ($p < 0.001$ vs. PBO) - Breast tenderness similar to PBO and BZA and significantly lower than HT ($p < 0.01$) - Adverse event rates were similar among the groups - Serious AEs overall and AE-related discontinuation rates lower than HT

ed for the time to fall asleep, sleep disturbance, and sleep adequacy at week 12 in comparison to placebo. CEE/BZA appears to affect sleep more directly in women who have severe VMS but more indirectly via improvements in VMS in women with less severe VMS [15,16].

Quality of life

The impact on the quality of life was assessed using the Menopause-Specific Quality of Life, a questionnaire with 29 items and four domains: vasomotor, psychosocial, physical, and sexual function. There were significant improvements in vasomotor scores and total score in women with treatment compared with placebo at 3, 12 and 24 months. In the SMART-3 study, which enrolled women with moderate or severe vulvar-vaginal atrophy (VVA), both doses of CEE/BZA also were associated with significant improvements on the sexual function domain compared with placebo [11]. In a SMART 5 sub-study that included 459 women who had severe vasomotor symptoms, improvements were similar to women treated with classic hormone therapy in hot flashes, sleep quality, and quality of life after 1 year of treatment [15].

Genitourinary syndrome

Low levels of estrogens and higher vaginal pH during menopause can result in Genitourinary menopause syndrome which include vaginal dryness, irritation of the vulva, burning, dysuria, dyspareunia... The action of the TSEC on vaginal tissue was studied in the SMART-3 trial [11]. Data from vaginal smears showed that the TSEC significantly increased the number of superficial and intermediate cells while decreasing the percentage of parabasal cells. This, can improve menopausal vaginal atrophy. The authors concluded that TSEC was efficient for the treatment of moderate and severe VVA in menopausal women. Sexual function was evaluated in the SMART-3 trial with the MENQoL and the Arizona Sexual Experiences Scale. Sexual function improved with any CEE/BZA dose compared with placebo and BZA alone; significant improvement were note in excitation, orgasm, and lubrication domains.

Bone tissue

Postmenopausal women are at increased risk for bone loss, osteoporosis, and fracture. Given separately, CEE and BZA are each protective against loss of bone mineral density and fracture in postmenopausal women [17,18]. The efficacy of the TSEC for the prevention of osteoporosis was assessed in SMART-1 and SMART-5 [9,13]. The SMART-1 trial included 2 Osteoporosis Prevention sub-studies: Participants in sub-study I were women with more than 5 years of menopause with Osteopenia plus 1 other osteoporosis risk factor, and participants in Substudy II were women in the first 5 years of menopause (when the rate of bone loss is greatest) and had at least 1 osteoporosis risk factor. The endpoint was bone mineral density changes at the lumbar spine and total hip [19]. In both SMART-1 sub-studies, all doses of CEE/BZA significantly increased the bone mineral density of the lumbar spine and hip after 2 years of treatment compared with placebo, similar to raloxifene or BZA in monotherapy. The changes were greater with combined hormone therapy with estrogen and progesterone. There were also changes in bone metabolism markers (osteocalcin as bone formation marker and C-telopeptide as serum resorption marker). The study investigators concluded that CEE/BZA decreases bone turnover and bone loss in postmenopausal women with increased osteoporosis risk. In a combined analysis of SMART-1 and -5, TSEC increased lumbar and hip Bone mineral density compared with placebo, independently of user risk, using the Fracture Risk Assessment Tool (FRAX) [20]. However, in Spain, CEE/BZA has not been approved for the treatment of postmenopausal osteoporosis [21].

Effects on endometrial tissue

Endometrial safety was widely studied in the SMART trials. Bazedoxifene showed to be neutral or antagonic in the endometrium. The minimum effective dose of BZA for preventing hyperplasia at 2 years was 20 mg [22]. In SMART-1, the endometrial thickness by ultrasound and incidence of endometrial hiperplasia over 2 years with any dose of CEE /BZA, was lower than 1%, similar to placebo [9]. In a study combining the five SMART trials, the findings of the endometrial biopsies, ultrasounds, and daily bleeding records were analyzed together. The rate of endometrial hyperplasia was maintained below 1%. Only one case of endometrial carcinoma with CEE/BZA was reported, in a women with many risk factors [23].

Effects on breast tissue

CEE showed a protective effect against breast cancer given without a progestin in the WHI trial. Administered alone, BZA has been associated with an incidence of breast cancer similar to placebo with a follow-up of 7 years [24]. The data obtained in laboratory studies reveal that BZA in combination with CE exerts an anti-estrogenic effect on breast tissue [25]. In clinical studies, the incidence of breast cancer in more than 3700 women treated with CE/BZA was the same as that observed with placebo at 2 years of follow-up. No changes were observed in the radiological density, mastodynia, or benign pathology [26]. Thus, CE/BZA offers a better breast tolerability profile than hormone therapy with estrogens and progesterone, which has been associated with breast pain and increased breast density.

Cardiovascular effects

EC and BZA increase the incidence of thrombotic events separately. The risk is higher during the first year of treatment. In the SMART trials, the incidence of thrombotic events was low compared with placebo with six recorded cases out of 4868 treated women. Similarly, among users of CEE/BZA, the incidence of ictus,

ischemic heart disease and myocardial infarction was similar among users of treatment and placebo. A meta-analysis of all five SMART trials evaluated cardiovascular safety data: It concluded that for up to 2 years of treatment, TSEC present an acceptable cardiovascular safety profile with rates of stroke and coronary artery disease similar to placebo in healthy postmenopausal women. Also, the risk of venous thromboembolism was low [27].

Tolerability

The most frequent adverse effect was abdominal pain (greater than 10% of patients) followed by vulvovaginal candidiasis, constipation, diarrhea, nausea and muscle spasms. Triglycerides were increased until 15% [28].

Conclusions

Overall, data from the literature demonstrates that the TSEC significantly reduces vasomotor symptoms and increases the quality of sleep (improving the quality of life), protecting also bone tissue and vaginal atrophy. It does not stimulate breast and endometrial tissue and does not increase cardiovascular risk.

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