European Review for Medical and Pharmacological Sciences 2016; 20: 3934-3944

Ospemifene: a safe treatment of vaginal atrophy

L. DEL PUP

Gynecological Oncology, Centro di Riferimento Oncologico, IRCCS - National Cancer Institute, Aviano (PN), Italy

Abstract. – OBJECTIVE: Vaginal atrophy is a chronic, progressive medical condition that affects fifty percent of postmenopausal women, causing symptoms like dyspareunia, vaginal dryness, and vaginal irritation. Until recently, the only prescription options were systemic and vaginal estrogen therapies that might be limited by concerns about long-term safety and breast cancer risk. The objective is to analyze the literature about ospemifene, a tissue-selective estrogen receptor modulator (SERM) recently approved for the treatment of vulvovaginal atrophy and dyspareunia and to compare its effects with those of the other SERMs to assess its safety.

MATERIALS AND METHODS: Review. Medline search.

RESULTS: Ospemifene treats vaginal atrophy, and, if compared with other SERMS, it has no or not significant effects on endometrium and thromboembolism. Experimental and animal models suggest an inhibitory effect on the growth of malignant breast tissue. The available clinical data support ospemifene breast safety.

CONCLUSIONS: Ospemifene relieves moderate to severe symptoms of vulvovaginal atrophy, like dryness, irritation and soreness around the genital area, and painful sexual intercourse, in menopausal women. It is well tolerated, and it has neutral effects on endometrium and coagulation. Clinical trials and even long-term studies on breast cancer effects support ospemifene overall safety.

Key Words:

Ospemifene, Tamoxifen, Raloxifene, Bazedoxifene, SERM, Vaginal atrophy, Endometrial cancer, Breast cancer, Bone density, Thromboembolism.

Introduction

Vaginal atrophy has been treated for decades with local estrogens. Some of them have demonstrated a very low local absorption[1,2] but still some concern exists mostly for breast cancer patients which have a precocious and strong atrophic symptoms[3].

Vaginal atrophy impairs quality of life in most menopausal women[4], but the management of vaginal dryness is particularly frequent e difficult in estrogen sensitive cancer patients[5].

While there are effective, placebo-controlled, non-hormonal treatments for hot flushes[6], vaginal moisturizes have been till now the only treatment which is considered safe. Unfortunately, they are not satisfying if used alone with no proper estrogenic stimulation of vaginal epithelium[7].

A new class of drugs like selective estrogen receptor modulators (SERMs) can now offer a safe and effective treatment of vaginal atrophy bypassing those problems. They are synthetic non-steroidal agents that exhibit tissue-specific estrogens' receptor (ER) agonist or antagonist activity[8].

Each SERM has the ability to induce distinct structural changes in the receptor that influence the interaction with coactivators (CoA) or co repressors (CoR), which are involved in the regulation of target gene transcription. The resulting biologic action can vary according to the specific type of ER, co-factors, responses and ligands leading to tissue-specific agonist and antagonist activity. Different ligands can induce distinct receptor conformations in ER and ERβ, leading to structures that are different than those seen with an unliganded receptor.

SERMs can exert a wide range of physiological effects related to both pathological and therapeutic processes, with unique and often distinctly different patterns of ER subtype expression seen in different tissues. They are used for various indications, including treatment of vaginal atrophy, breast cancer, osteoporosis, and ovulation induction.

Based on their efficacy and long-term safety, SERMs are being increasingly prescribed. Ospemifene is a novel SERM, a triphenylethylene derivative, that is structurally similar to tamoxifen, but without the 2-(dimethylamino)ethoxy region, making it safe for the endometrium, ef-

Corresponding Author: Lino Del Pup, MD; e-mail: ldelpup@cro.it

fective for alleviating vaginal atrophy symptoms and according to the available data still protective, or at least neutral, for the breast and with no effect on coagulation. The present review aims at helping clinicians understanding the role and safety of ospemifene comparing it with the other SERMS.

Materials and Methods

A Medline search has been performed till August 2016 using this strategy: ("Ospemifene" [Supplementary Concept] OR ospemifene[ti]) AND atrophy[mh]) OR ((Tamoxifen/adverse effects[Majr] OR Tamoxifen/toxicity[majr] OR Tamoxifen/therapeutic use[majr] OR Tamoxifen/pharmacology[majr] OR Toremifene/adverse effects[Majr] OR Toremifene/TOXICITY[Majr] OR Toremifene/therapeutic use[Majr] OR Toremifene/pharmacology[Majr]) AND Breast Neoplasms[MAJR]) OR ((Raloxifene Hydrochloride/adverse effects[majr] OR Raloxifene Hydrochloride/TOXICITY[majr] OR Raloxifene Hydrochloride/therapeutic use[majr]) AND Osteoporosis[Mh]) OR (Bazedoxifene/ADVERSE EFFECTS[majr] OR Bazedoxifene/therapeutic use[majr]) OR (Selective Estrogen Receptor Modulators/adverse effects[Majr] OR Selective Estrogen Receptor Modulators/contraindications[Majr] OR Selective Estrogen Receptor Modulators/therapeutic use[Majr] OR Selective Estrogen Receptor Modulators/toxicity[Majr])) AND (ita[la] OR eng[la]) AND (review[pt] OR systematic[sb] OR "Thrombosis"[Mesh] OR thrombos*[tiab] OR thrombot*[ti] OR "Endometrium/drug effects"[Mesh] OR "Uterine Diseases/chemically induced"[Mesh] OR "Ovary/drug effects"[Mesh] OR "Ovarian Diseases/chemically induced"[Mesh])) NOT (male[ti] OR men[ti]). Other literature has been collected using the following keywords: ospemifene, tamoxifen, raloxifene, bazedoxifene, SERM, vaginal atrophy, endometrial cancer, breast cancer, bone density, thromboembolism.

Results and Discussion

SERMs show mixed agonist and antagonist activities depending on the target tissue. Triphenylethylene SERMs, considered as first generation SERMs, include tamoxifen and toremifene which are approved to prevent and treat breast cancer. Benzothiophene SERMs, considered as second-generation SERMs, include raloxifene which is approved for the prevention of breast cancer and the prevention and treatment of osteoporosis. Third-generation SERMs include bazedoxifene and ospemifene, which also have antagonistic-antiestrogenic effects on the breast[9].

Bazedoxifene is approved in combination with conjugated equine estrogens to treat vasomotor symptoms and preventing osteoporosis. Ospemifene is approved for the treatment of moderate to severe symptoms of vulvovaginal atrophy (dryness, irritation and soreness around the genital area, and painful sexual intercourse) in menopausal women (check EMEA approval).

Breast and endometrial cancer safety, and thromboembolic effects are key differentiators among SERMs in clinical practice. For example, tamoxifen exhibits ER agonist activity in the uterus, resulting in an increased risk of endometrial hyperplasia and malignancy, whereas ospemifene, raloxifene and bazedoxifene have neutral effects on the uterus[10].

SERMs as a class appear to have an increased risk of venous thromboembolism (VTE) similar to estrogens, although available data on ospemifene are reassuring[11].

Until large randomized controlled trials (RCTs) with cardiovascular primary endpoints are performed, potential cardioprotective benefits of SERMs will remain unclear. Central nervous system effects are variable and not well defined. There is some evidence of decreased effect on pro-inflammatory markers in women at neurodegenerative risk. SERMs as a class have shown an estrogen antagonist effect with a mild increase in hot flashes, generally not enough significant to discontinue therapy

Tamoxifen, raloxifene and bazedoxefine have no direct positive effects on the vagina, while ospemifene has them as the main beneficial effect[12].

Most of the data on SERMs-relative estrogen receptors antagonistic or agonistic effects can be species-dependent and come from preclinical data; therefore, any interpretation and comparison of preclinical *vs*. human findings must be made with caution. The strength of the antagonist and agonist effect of ospemifene compared with other SERMS in (A) Bone (B) endometrium and (C) breast are represented in Figure 1.

An overview of the comparative effects of the most used SERMS and their main indications are summarized in Table I and described in detail in the following paragraphs.

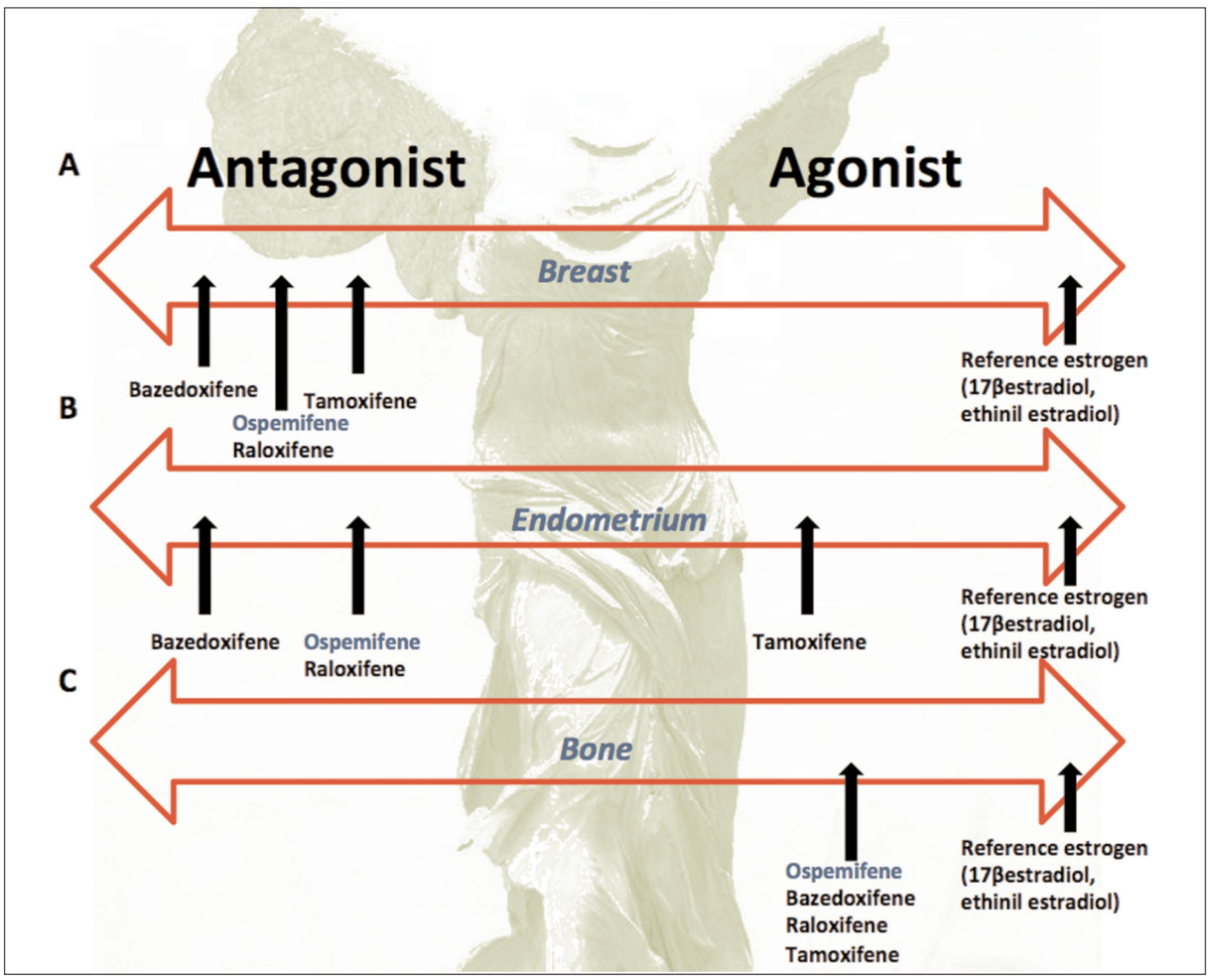

Figure 1. Strenght of the antagonist and agonist effect of ospemifene compared with other SERMS in ***(A)*** Breast ***(B)*** Endometrium and ***(C)*** Bone. (Modified from Komm BS, Mirkin SJ. An overview of current and emerging SERMs. Steroid Biochem Mol Biol 2014; 143: 207-222).

OSPEMIFEN: *Vaginal Atrophy*

Ospemifene is, as a SERM, an estrogen-receptor agonist/antagonist approved for the treatment of moderate-to-severe dyspareunia, a symptom of vulvovaginal atrophy, caused by menopause. It is a triphenylethylene derivative, structurally similar to tamoxifen, but without the 2-(dimethylamino)ethoxy region. Removal of this region has been associated with reduced agonistic activity in the uterus, and no effects on agonist activity in the cardiovascular system, explaining its putative neutral thromboembolic effect.

Table I. Overview of the comparative effects of the most used SERMS and their main indications.

	Vagina	Endometrium	Breast	Bone	Venous thromboembolism	Main indication
Ospemifene	+++	=	--	++	=	Vaginal Atrophy
Tamoxifen	=	++	---	++	++	Breast cancer Prevention
Raloxifene	=	=	--	+++	+	Osteoporosis
Bazedoxifene	=	=/-	--	++	+	Menopause (+ Conjugated Equine Estrogens)

+: agonistic/stimulatory effect; -: antagonistic/inhibitory effect; =: neutral.

The binding affinity of ospemifene for ER and ERβ has been evaluated in a competitive binding assay. Ospemifene has displaced labeled 17β-estradiol in a concentration-dependent manner, with relative binding affinities of 0.8% and 0.6% for ER and ERβ, respectively[13] and it is comparable to 4-OH tamoxifen with a better safety profile because ospemifene does not have an endometrial stimulatory effect[14].

Vagina

The most distinguishing effect of ospemifene is its significant estrogenic effect on vaginal epithelium[15]. This is evidenced by an increase in intermediate and superficial cells in repeated Pap smears[16].

Ospemifene estrogenic effect on the vaginal epithelium, improves vaginal maturation index (VMI), vaginal pH, dryness and dyspareunia[17].

The estrogenic effect on the vaginal epithelium of the treatment with ospemifene 30-90 mg for 3 months has been also demonstrated in a study on 119 patients with the disappearance of parabasal cells and the appearance of intermediate and superficial cells, in contrast to the raloxifene treatment, which has been resulting in no changes. There has been no associated endometrial stimulation.

Also, the Kupperman index of climacteric symptoms and visual analog scale scores for vasomotor symptoms have been decreasing in this study[18] but not in another[19].

826 women have been randomized to receive ospemifene 30 mg, 60 mg, or placebo once daily in a 12-week study[20]. Ospemifene 30 or 60 mg significantly increased the percentage of superficial cells, significantly decreased the percentage of parabasal cells and decreased vaginal pH ($p < 0.001$ for each group relative to placebo). By week 4 of treatment, a significant improvement in the maturation index has been observed for both ospemifene groups compared with placebo ($p < 0.001$). The use of ospemifene 60 mg significantly reduced dyspareunia by 12 weeks, also ospemifene 30 or 60 mg significantly decreased vaginal dryness in the same period.

In another 12-week phase III trial, 605 postmenopausal women with vulvovaginal atrophy have been randomized to ospemifene 60 mg or placebo once daily[21].

Compared with placebo, ospemifene treatment has significantly reduced dyspareunia ($p = 0.0001$), has increased the percentage of superficial cells ($p < 0.0001$), has decreased the percentage of parabasal cells ($p < 0.0001$), and has decreased vaginal pH ($p < 0.0001$).

Ospemifene has received its first marketing approval for the treatment of dyspareunia in postmenopausal women in February 2013 by the FDA[22] and then in November 2014 by the EMEA with the indication to treat moderate to severe symptoms of vulvovaginal atrophy (dryness, irritation and soreness around the genital area, and painful sexual intercourse) in women who have been through menopause. It is used in women who cannot use locally applied estrogen therapy.

Endometrium

Ospemifene has no clinically significant endometrial effects based on transvaginal ultrasonography and biopsies, in comparison to raloxifene (thought to be neutral on the endometrium) and tamoxifen (known to stimulate endometrial tissue).

In a phase III study of postmenopausal women receiving ospemifene 30 or 60 mg or placebo for up to 12 weeks, the mean change from baseline for endometrial thickness has been 0.42, 0.72, and −0.02 mm for ospemifene 30 mg, ospemifene 60 mg, and placebo, respectively[20].

In a randomized, double-blind, placebo-controlled, parallel group study, women aged 40 to 80 years with VVA and an intact uterus, have been randomized 6:1 to receive ospemifene 60 mg/day or placebo. The primary objective was 12-month safety, particularly endometrial[23].

Safety assessments included endometrial histology and thickness, breast and gynecological examinations. Efficacy evaluations included changes from baseline to week 12 in the percentage of superficial and parabasal cells and vaginal pH. Of the 426 randomized subjects, 81.9% completed the study, being adverse events as the most common reason for discontinuation (ospemifene 9.5%; placebo 3.9%). Most (88%) treatment-emergent adverse events in the ospemifene arm were considered mild or moderate. Three cases (1.0%) of active proliferation were observed in the ospemifene group. For one, active proliferation was seen at the end of study (week 52), and, on a follow-up biopsy 3 months after the last dose, was diagnosed as a simple hyperplasia without atypia. This subsequently resolved with progestogen treatment and dilatation and curettage. In six subjects (5 ospemifene [1.4%] and 1 placebo [1.6%]) endometrial polyps have been found (histopathology); however, only one (in

the ospemifene group) has been confirmed as a true polyp during the additional expert review. Endometrial histology showed no evidence of carcinoma. Statistically significant improvements with ospemifene *vs*. placebo have been seen for all primary and secondary efficacy measures and have been sustained through week 52.

Ospemifene showed no endometrial stimulation effect in a previous study too[18].

There has been also no effect of ospemifene on the appearance of proliferation marker Ki-67 in the endometrium as compared with placebo, and endometrial thickness increased only by mean 0.4 to 0.6 mm ($p = 0.05$), perhaps as a result of increased uterine blood flow[16, 24].

Breast

Ospemifene has shown inhibiting effects on breast tissue in both experimental, animal and preliminary human clinical data.

Animal models with ospemifene suggest an inhibitory effect on the growth of malignant breast tissue, and clinical trials, including three long-term studies assessing the overall safety of ospemifene, supporting that ospemifene is usually well tolerated, with neutral effects on the breast, no significant effects on the endometrium and beneficial effects on the vagina[9].

Breast Safety Experimental and Animal Studies

Experimental *in vitro* and animal studies concordantly support the breast safety of ospemifene[25-27].

In rat and human mammary cells *in vitro*, ospemifene evokes a dose-dependent inhibition on estrogen-induced cell responses and cell proliferation, supporting an antiestrogenic effect in the breast[28].

The expression of pS2, an estrogen marker, is suppressed and the tumor growth is inhibited in a dose-dependent manner by ospemifene (12%, 59%, and 79%-88% in the 1-, 10-, and 50- mg/kg groups, respectively)[13].

The growth of ER-dependent MCF-7 cells with no effect on ER-independent MDA-MB-231 cells is inhibited by ospemifene[29].

Ospemifene significantly reduces 7,12-Dimethylbenz[a]anthracene (DMBA)-induced mammary carcinomas, similarly to tamoxifen 30.

The growth of transplanted cells and occurrence of tumors have been significantly reduced in mice treated with either ospemifene or tamoxifen compared with untreated mice[26].

Ospemifene has delayed the development of breast tumors, and average tumor volumes were smaller[31].

Ospemifene has been found to be toxic to MCF-7 cell lines and not on MDA-MB-231 cell lines so new structural analogs of ospemifene are screened for their activity against MCF-7 (ER-positive) and MDA-MB-231 (ER-negative) human breast cancer cell lines. The compounds containing more polar groups like amine and amide are more potent than ospemifene against MCF-7 cells and are better even in the case of non-estrogen dependent MDA-MB-231 cells. High potency in the case of amines and amides could be due to their improved hydrogen bonding abilities[32].

Ospemifene and tamoxifen are anti-breast cancer agents' precursors of other analogs against ER-positive (MCF-7) and ER-negative (MDA-MB-231) human breast cancer cell lines that are in development[33].

If compared with the other SERMs, it has been reported that the presence of chlorine group in ospemifene reduces the antiestrogenic activity and the introduction of azide group in some organic molecules enhances the anticancer activity[34].

Breast Safety Data on Humans

The overall long-term breast safety of ospemifene has been assessed also in humans[35,36].

An initial 12-week study has been evaluating the efficacy and tolerability of ospemifene 30 mg/d and 60 mg/d in 826 women (ospemifene 30 mg, n 282; ospemifene 60 mg, n 276; placebo, n 268)[20]. After completing the initial study, women with a uterus were eligible to continue a blinded treatment for a total of 52 weeks (12 weeks in the initial study plus 40 weeks in the safety extension [N180]). Safety assessments of the breast included mammograms and palpation on a physical examination performed at week 52 or at study discontinuation[37].

The majority of breast palpations at week 52 had normal results, and the findings were similar for all the study groups (normal results: 100% for placebo, 100% for ospemifene 30 mg/d, and 98.3% for ospemifene 60 mg/d). Furthermore, results of mammograms performed at week 52 were normal for all the subjects in all study groups, with the exception of one subject in the ospemifene 60-mg/d group who had an abnormal mammogram finding that subsequently resolved during follow-up after completion of the study.

Only two subjects experienced a serious treatment-emergent adverse event breast-related: one (2%) subject in the placebo group had breast cancer in situ, and one (1.4%) subject in the ospemifene 60-mg group had breast prosthesis implantation surgery. Six subjects experienced a non-serious breast-related event: 2.0% in the placebo group had a breast cyst; 3.2% in the ospemifene 30-mg/d group had evidence of a breast mass; and 4.3% in the ospemifene 60-mg/d group had a breast mass, breast microcalcification, or an abnormal mammogram (as noted previously). All six non-serious breast-related events were mild in severity.

A randomized, double-blind, placebo-controlled study[38] has evaluated the safety and the efficacy of ospemifene 60 mg over 52 weeks in 426 women with VVA and an intact uterus (ospemifene, n 363; placebo, n 63).

Breast safety has been assessed by palpation at screening, then at weeks 12, 26, 52, and at the post-treatment follow-up visit (< 4 weeks after treatment completion). Mammography has been conducted at screening and week 52 or end of treatment. No clinically significant changes from baseline to week 52 have been noted on breast examination or mammography for any study participant at any time. No cases of breast cancer have occurred during this study.

Similar breast safety results have been achieved in a long-term, open-label safety extension of the same initial 12-week study. In this assessment of women without a uterus treated with ospemifene 60 mg/d for 52 weeks, no clinically significant changes in overall breast safety have been observed at week 26 or week 52 (N ¼ 301; data on file). All breast-related TEAEs have been considered mild or moderate in severity. One subject in the ospemifene group had a report of a breast-related TEAE (breast mass), assessed as mild and unlikely related to the study drug, and still ongoing at the end of the study and at the 4-week follow-up visit. Subsequent mammograms during routine care visits after study completion have been reported to be normal.

Bone

Ospemifene has bone protective effects, both in preclinical and in clinical studies[39]. It has an estrogenic effect on bone, as seen by improved bone mineral density, strength, mass, and histomorphometry in preclinical models, consistent with improvements in markers of bone resorption and formation in postmenopausal women.

In ovariectomized rats, ospemifene 10 mg/kg prevented an ovariectomy-induced reduction in total tibial weight, prevented the ovariectomy-induced loss of bone strength in the femoral neck and lumbar vertebrae, and normalized histomorphometric parameters in the direction of the control values, with effects similar to those achieved with 17β-estradiol 50 g/kg[13].

Ospemifene in clinical setting decreased the levels of bone resorption markers[40].

Ospemifene has effects on bone turnover markers comparable with raloxifene 60 mg/day in a randomized, double-blind study on postmenopausal women[41].

Ospemifene decreased bone resorption in a dose-dependent manner, as demonstrated by the decreases in the levels of urinary N-telopeptide (NTX; $p < 0.05$ for all doses *vs*. placebo) and a fall in the level of urinary C-telopeptide (CTX) with ospemifene 90 mg ($p < 0.05$ *vs*. placebo). A dose-dependent decrease in bone formation markers procollagen type I N propeptide (PINP; $p < 0.05$ and $p < 0.01$, respectively) and alkaline phosphates (ALP; both $p < 0.05$ *vs.* placebo) have also been seen with ospemifene 60 and 90 mg [40].

Venous Thromboembolism

Ospemifene seems neutral or partial agonistic on venous thromboembolism. Only one case of venous thromboembolism has been noted in long-term safety studies.

Overall, the prevalence rates per thousand women of thromboembolic events with ospemifene 60 mg in clinical trials (duration of treatment of up to 15 months) have been 0.72 (thromboembolic stroke; 1 case), 1.45 (hemorrhagic stroke; 2 cases), and 1.45 (deep vein thrombosis [DVT]; 2 cases), whereas for placebo these rates have been 1.04 (1 case), 0 (no cases), and 1.04 (1 case), respectively. The absolute numbers are very small and comparable to placebo. Therefore, the warning of potential venous thrombosis on ospemifene label can be considered only a class effect[42].

TAMOXIFEN: Breast Cancer Prevention

Tamoxifen is widely used for its antagonistic effects on breast to prevent and treat invasive breast cancer: reduction of invasive breast cancer in women with ductal carcinoma in situ (DCIS) after surgery and radiation therapy; treatment of metastatic breast cancer; adjuvant treatment of

breast cancer; and reduction of breast cancer incidence in high-risk women. For women who have ER-positive breast cancer, tamoxifen has been shown to reduce the risk of recurrence and death when used as adjuvant therapy in early stage disease or as palliation for those with metastatic cancer[10].

Its agonistic further beneficial actions are: increased bone mass density, decreased fracture rates improved cholesterol, and decreased cardiovascular morbidity. Unfortunately, it causes endometrial stimulation, increasing the risk of endometrial carcinoma including the mixed mesodermal type. Other limits are the venous thromboembolic effect and the increased risk of pulmonary embolism.

Another triphenylethylene SERMs, considered as the first generation, is toremifene approved to prevent and to treat breast cancer. Toremifene has similar effects but less endometrial stimulation than tamoxifen[43].

Vagina

Tamoxifen has a mixed effect on the vagina. Although estrogenic vaginal effects have been noted with tamoxifen, adverse vaginal effects during treatment have also been reported, including dyspareunia, leucorrhea, and vaginal dryness[42].

Endometrium

Tamoxifen estrogenic activity on endometrial tissue results in an increased rate of endometrial hyperplasia and risk of endometrial cancer[44]. The endometrial cancer risk with tamoxifen 20 mg/day *vs*. placebo is increased from relative risk (RR) 2.53 (95% CI, 1.35-4.97)[45] to as high as RR 7.5 [95% CI, 1.7-32.7] in women with breast cancer[46].

While tamoxifen exhibits ER agonist activity in the uterus, resulting in an increased risk of endometrial hyperplasia and malignancy, ospemifene, raloxifene and bazedoxifene demonstrate none or minimal clinically meaningful effect on the uterus[47].

Breast

Tamoxifen has an antiestrogenic effect in the breast. In rat models of induced mammary tumors, it causes a delayed appearance of the diseases, reduces the total number of resulting tumors, and causes tumor regression. Clinically it reduces invasive breast cancer risk to 49% reduction with tamoxifen 20 mg/day *vs*. placebo[45].

Bone

Tamoxifen has estrogen agonist effects on bone, resulting in the preservation of bone mineral density (BMD) in postmenopausal women. Lumbar BMD increases 0.61% per year with tamoxifen 10 mg/day *vs*. 1% decrease with placebo[48].

The RR of hip fracture is 0.55; 95% CI, 0.25-1.15 with tamoxifen 20 mg/day *vs*. placebo[45].

Venous Thromboembolism

Tamoxifen increases both venous thromboembolic and pulmonary embolism risks. This is the main limit to long-term continuation beyond 10 years, versus 5 years, of adjuvant tamoxifen therapy: the RR of pulmonary embolism is 1.87 (95% CI 1.13-3.07, $p = 0.01$)[49].

A review of tamoxifen in large RCTs has suggested cardioprotective effects with improved lipid profiles in women, but cardiovascular outcomes are challenging to interpret[50,51].

RALOXIFENE: Osteoporosis Prevention

Raloxifene hydrochloride is a selective estrogen receptor modulator that has antiestrogenic effects on breast and endometrial tissue and estrogenic effects on bone, lipid metabolism, and blood clotting. Raloxifene increases the bone mass density, prevents vertebral fractures and improves lipid profile.

Vagina

Raloxifene has a neutral effect on vagina[52].

Endometrium

Raloxifene does not increase the risk of endometrial cancer (RR, 0.8; 95% CI, 0.2-2.7)[53].

Breast

Raloxifene prevents invasive ER-positive breast cancer. This is demonstrated in CORE, STAR and MORE[53] trial, where breast cancer RR is 0.35; 95% CI, 0.21-0.58 with raloxifene 60 or 120 mg *vs*. placebo.

Bone

Raloxifene has become the first SERM to receive FDA regulatory approval for osteoporosis[54,55].

Venous Thromboembolism

Raloxifene increases the risk of VTE and fatal stroke[56].

BAZEDOXIFENE: Treatment of Menopausal Hot Flashes and Prevention of Bone Loss (if Combined With CEE)

Bazedoxifene (BZA) is a SERM which is not used alone, but in a tissue-selective estrogen complex (TSEC), combined with conjugated equine estrogen (CEE), as a novel strategy of menopausal hormone therapy without involving any progestin[57].

It also allows for the estrogenic benefits on relief of hot flashes and prevention of bone loss without stimulating the breast or the endometrium.

Vagina

Bazedoxifene has a neutral effect on vagina[58].

Endometrium

Bazedoxifene alone does not increase endometrial thickness or rates of endometrial hyperplasia or cancer[59,60].

The pairing with CEE reduces the risk of endometrial hyperplasia that can occur with the estrogenic component of the TSEC without the need for a progestogen in women with a uterus.

Breast

The effect of bazedoxifene on the breast is neutral to antagonist[61].

It significantly lowers the incidence of fibrocystic breast disease ($p \leq 0.05$)[60].

The combined effect of bazedoxifene + CEE seems neutral: no breast tenderness or changes in breast density. It warrants further studies for breast cancer effect.

Bone

Bazedoxifene is associated with a reduced rate of vertebral fracture *vs*. placebo ($p < 0.05$)[59]

Venous Thromboembolism

Venous thromboembolic events (pulmonary embolism, retinal vein thrombosis, deep vein thrombosis, and thrombophlebitis) are rare, occurring in less than 1 per 1000 patients treated with CEE+ bazedoxifene[62].

Conclusions

About fifty percent of menopausal women suffer from vaginal atrophy which symptoms include vaginal dryness, irritation, itching, soreness, burning, dyspareunia, discharge, urinary frequency and urgency. Despite the high prevalence and the substantial effect on quality of life, vulvovaginal atrophy often remains underreported and undertreated[63].

The main reason is the fear of the breast cancer effects of estrogens[64-66]. Cancer patients suffer more from vaginal atrophy[67], and they have different questions and needs related to sexuality and fertility[68,69].

The available clinical data for ospemifene, including long-term safety evaluations in postmenopausal women with vulvovaginal atrophy, support a neutral effect on endometrium, breast and thromboembolism. In particular, investigations in animal models suggest that ospemifene may have an inhibitory effect on the growth of malignant breast tissue. The other SERMS have not such a beneficial vaginal effect. All of them are beneficial for the bone, as ospemifene, but tamoxifen increases endometrial cancer risk and, as raloxifene and bazedoxifene, it may increase venous thrombotic risk. These data make ospemifene a valuable tool for those women who suffer from vaginal climacteric symptoms, and are afraid of or cannot use local estrogens.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Del Pup L, Postruznik D, Corona G. Effect of one-month treatment with vaginal promestriene on serum estrone sulfate levels in cancer patients: a pilot study. Maturitas 2012; 72: 93-94.
2) Del Pup L, Di Francia R, Cavaliere C, Facchini G, Giorda G, De Paoli P, Berretta M. Promestriene, a specific topic estrogen. Review of 40 years of vaginal atrophy treatment: is it safe even in cancer patients? Anticancer Drugs 2013; 24: 989-998.
3) Del Pup L, Salvagno F, Revelli A, Guido M, Castello C, Borini A, Peccatori F. Gonadotoxic effects of breast cancer treatment and fertility protection strategies: evidence based answers to the main questions the patients ask WCRJ 2014; 1: e409.
4) Donati Sarti C, Graziottin A, Mincigrucci M, Ricci E, Chiaffarino F, Bonaca S, Becorpi A, Cipriani S, Parazzini F; Gruppo di studio IperAOGOI. Correlates of sexual functioning in Italian menopausal women. Climacteric 2010; 13: 447-456.
5) Del Pup L. Management of vaginal dryness and dyspareunia in estrogen sensitive cancer patients. Gynecol Endocrinol 2012; 28: 740-745.

6) Del Pup L, Maggino T. Non-hormonal treatment of vasomotor symptoms in gynecological cancer patients. Eur J Gynaecol Oncol 2010; 31: 299-303.

7) Del Pup L. Treatment of atrophic and irritative vulvovaginal symptoms with an anhydrous lipogel and its complementary effect with vaginal estrogenic therapy: new evidences. Minerva Ginecol 2010; 62: 287-291.

8) Komm BS, Mirkin S. An overview of current and emerging SERMs. J Steroid Biochem Mol Biol 2014; 143: 207-222.

9) Berga SL. Profile of Ospemifene in the breast. Reprod Sci 2013; 20: 1130-1136.

10) Maximov PY, Lee TM, Jordan VC. The discovery and development of selective estrogen receptor modulators (SERMs) for clinical practice. Curr Clin Pharmacol 2013; 8: 135-115.

11) Pinkerton JV, Thomas S. Use of SERMs for treatment in postmenopausal women. J Steroid Biochem Mol Biol 2014; 142: 142-154.

12) Simon JA, Lin VH, Radovich C, Bachmann GA, Ospemifene Study Group. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause 2012; 20: 418-427.

13) Qu Q, Zheng H, Dahllund J, Laine A, Cockcroft N, Peng Z, Koskinen M, Hemminki K, Kangas L, Vaananen K, Harkonen P. Selective estrogenic effects of a novel triphenylethylene compound, FC1271a, on bone, cholesterol level, and reproductive tissues in intact and ovariectomized rats. Endocrinology 2000; 141: 809-820.

14) Gennari L, Merlotti D, Valleggi F, Nuti R. Ospemifene use in postmenopausal women Expert Opin Investig. Drugs 2009; 18: 839-849.

15) Unkila M, Kari S, Yatkin E, Lammintausta R. Vaginal effects of ospemifene in the ovariectomized rat preclinical model of menopause. J Steroid Biochem Mol Biol 2013; 138: 107-115.

16) Rutanen EM, Heikkinen J, Halonen K, Komi J, Lammintausta R, Ylikorkala O. Effects of ospemifene, a novel SERM, on hormones, genital tract, climacteric symptoms, and quality of life in postmenopausal women: a double-blind, randomized trial. Menopause 2003; 10: 433-439.

17) Voipio SK, Komi J, Kangas L, Halonen K, DeGregorio MW, Erkkola RU. Effects of ospemifene (FC-1271a) on uterine endometrium, vaginal maturation index, and hormonal status in healthy postmenopausal women). Maturitas 2002; 43: 207-214.

18) Komi J, Lankinen KS, Harkonen P, DeGregorio MW, Voipio S, Kivinen S, Tuimala R, Vihtamaki T, Vihko K, Ylikorkala O, Erkkola R. Effects of ospemifene and raloxifene on hormonal status, lipids, genital tract, and tolerability in postmenopausal women. Menopause 2005; 12: 202-209.

19) Simon JA, Lin VH, Radovich C, Bachmann GA. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause 2013; 20: 418-427.

20) Bachmann GA, Komi JO, the Ospemifene Study Group. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause 2010; 17: 480-486.

21) Portman DJ, Bachmann GA, Simon JA, the Ospemifene Study Group. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. Menopause 2013; 20: 623-630.

22) Traynor K. Pharmacy News Ospemifene approved for postmenopausal problem. American Society of Health-System Pharmacists web site, American Society of Health-System.

23) Goldstein SR, Bachmann GA, Koninckx PR, Lin VH, Portman DJ, Ylikorkala O, the Ospemifene Study Group. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. Climacteric 2014; 17: 173-182.

24) Constantine GD, Goldstein SR, Archer DF. Endometrial safety of ospemifene: results of the phase 2/3 clinical development program. Menopause 2015; 22; 36-43.

25) Wurz GT, Read KC, Marchisano-Karpman C, Gregg JP, Beckett LA, Yu Q, Degregorio MW. Ospemifene inhibits the growth of dimethylbenzanthracene-induced mammary tumors in Sencar mice. J Steroid Biochem Mol Biol 2005; 97: 230-240.

26) Namba R, Young LJ, Maglione JE, McGoldrick ET, Liu S, Wurz GT, DeGregorio MW, Borowsky AD, MacLeod CL, Cardiff RD, Gregg JP. Selective estrogen receptor modulators inhibit growth and progression of premalignant lesions in a mouse model of ductal carcinoma in situ. Breast Cancer Res 2005; 7: R881–888.

27) Gutierrez MC, Detre S, Johnston S, Mohsin SK, Shou J, Allred DC, Schiff R, Osborne CK, Dowsett M. Molecular changes in tamoxifen-resistant breast cancer: relationship between estrogen receptor, HER-2, and p38 mitogen-activated protein kinase. J Clin Oncol 2005; 23: 2469-2476.

28) Kangas L, Unkila M. Tissue selectivity of ospemifene: pharmacologic profile and clinical implications. Steroids 2013; 78: 1273-1280.

29) Taras TL, Wurz GT, DeGregorio MW. In vitro and in vivo biologic effects of ospemifene (FC-1271a) in breast cancer. J Steroid Biochem Mol Biol 2001; 77: 271-279.

30) Wurz GT, Soe LH, DeGregorio MW. Ospemifene, vulvovaginal atrophy, and breast cancer. Maturitas 2013; 74: 220-225.

31) Burich RA, Mehta NR, Wurz GT, McCall JL, Greenberg BE, Bell KE, Griffey SM, DeGregorio MW. Ospemifene and 4- hydroxyospemifene effectively prevent and treat breast cancer in the MTag.Tg transgenic mouse model. Menopause 2012; 19: 96-103.

32) Kaur G, Mahajan MP, Pandey MK, Singh P, Ramisetti SR, Sharma AK. Design, synthesis and evaluation of Ospemifene analogs as anti-breast cancer agents. Eur J Med Chem 2014; 86: 211-218.

33) Kaur G, Mahajan MP, Pandey MK, Singh P, Ramisetti SR, Sharma AK. Design, synthesis, and anti-breast cancer evaluation of new triarylethylene analogs bearing short alkyl- and polar amino-/amido-ethyl chains. Bioorg Med Chem Lett 2016; 26: 1963-1969.

34) Stygar D, Muravitskaya N, Eriksson B, Eriksson H, Sahlin L. Effects of SERM (selective estrogen receptor modulator) treatment on growth and proliferation in the rat uterus. Reprod Biol Endocrinol 2003; 1: 40.

35) Simon J, Bachmann G, Goldstein S, Lin V, Portman D, Phelps M. Evaluation of the safety of daily ospemifene 60 mg for up to 1 year when used in the treatment of vulvar and vaginal atrophy in postmenopausal women (abstract). Climacteric 2011; 14(suppl. 1): 87.

36) Simon J. Efficacy and safety of daily ospemifene 60 mg for up to 1 year when used in the treatment of vulvar and vaginal atrophy in postmenopausal women (abstract). Menopause 2012; 19: 1397-1398.

37) Simon J, Lin V, Radovich C, Bachmann GA, The Ospemifene Study Group. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause 2013; 20: 418-427.

38) Bachmann G, Goldstein S, Lin V, Simon J, Portman D, Phelps M. Efficacy of ospemifene when used in the treatment of vulvar and vaginal atrophy for up to 52 weeks in postmenopausal women. Climacteric 2011; 14 (suppl 1): 92.

39) Constantine GD, Kagan R, Miller PD. Effects of ospemifene on bone parameters including clinical biomarkers in postmenopausal women. Menopause 2016; 23: 638-644.

40) Komi J, Heikkinen J, Rutanen EM, Halonen K, Lammintausta R, Ylikorkala O. Effects of ospemifene, a novel SERM, on biochemical markers of bone turnover in healthy postmenopausal women. Gynecol Endocrinol 2004; 18: 152-158.

41) Komi J, Lankinen KS, DeGregorio M, Heikkinen J, Saarikoski S, Tuppurainen M, Halonen K, Lammintausta R, Vaananen K, Ylikorkala O, Erkkola R. Effects of ospemifene and raloxifene on biochemical markers of bone turnover in postmenopausal women. J Bone Miner Metab 2006; 24: 314-318.

42) Pinkerton JV, Stanczyk FZ. Clinical effects of selective estrogen receptor modulators on vulvar and vaginal atrophy. Menopause 2014; 21: 309-319.

43) Vogel CL, Johnston MA, Capers C, Braccia D. Toremifene for breast cancer: a review of 20 years of data. Clin Breast Cancer 2014; 14: 1-9.

44) Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. Gynecol Oncol 2004; 94: 256-266.

45) Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90: 1371-1388.

46) Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst 1994; 86: 527-537.

47) Pinkerton JV, Goldstein SR. Endometrial safety: a key hurdle for selective estrogen receptor modulators in development. Menopause 2010; 17: 642-653.

48) Love RR, Mazess RB, Barden HS, Epstein S, Newcomb PA, Jordan VC, Carbone PP, DeMets DL. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med 1992; 326: 852-856.

49) Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, Abraham M, Alencar VH, Badran A, Bonfill X, Bradbury J, Clarke M, Collins R, Davis SR, Delmestri A, Forbes JF, Haddad P, Hou MF, Inbar M, Khaled H, Kielanowska J, Kwan WH, Mathew BS, Mittra I, Muller B, Nicolucci A, Peralta O, Pernas F, Petruzelka L, Pienkowski T, Radhika R, Rajan B, Rubach MT, Tort S, Urrutia G, Valentini M, Wang Y, Peto R. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013; 381: 805-816.

50) Onitilo AA, Kar P, Engel JM, Glurich I. Long-term cardiac and vascular disease outcomes following adjuvant tamoxifen therapy: current understanding of impact on physiology and overall survival. Minerva Med 2013; 104: 141-153.

51) Berretta M, Di Francia R, Tirelli U. Editorial – The new oncologic challenges in the 3RD millennium WCRJ 2014; 1: e133.

52) Gizzo S, Saccardi C, Patrelli TS, Berretta R, Capobianco G, Di Gangi S, Vacilotto A, Bertocco A, Noventa M, Ancona E, D'Antona D, Nardelli GB. Raloxifene has a neutral effect (Update on raloxifene: mechanism of action, clinical efficacy, adverse effects, and contraindications. Obstet Gynecol Surv 2013; 68: 467-481.

53) Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M, Lippman ME, Black D, Glusman JE, Costa A, Jordan VC. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999; 281: 2189-2197.

54) Delmas NPD, Bjarnason DNH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, Draper M, Christiansen C. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine en-

dometrium in postmenopausal women. N Engl J Med 1997; 337: 1641-1647.

55) Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Gluer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial, Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999; 282: 637-645.

56) Collins P, Mosca L, Geiger MJ, Grady D, Kornitzer M, mewou-Atisso MG, Effron MB, Dowsett SA, Barrett-Connor E, Wenger NK. Effects of the selective estrogen receptor modulator raloxifene on coronary outcomes in the Raloxifene Use for The Heart trial: results of subgroup analyses by age and other factors. Circulation 2009; 119: 922-930.

57) Song Y, Santen RJ, Wang JP, Yue W. Effects of the conjugated equine estrogen/bazedoxifene tissue-selective estrogen complex (TSEC) on mammary gland and breast cancer in mice. Endocrinology 2012; 153: 5706-5715.

58) Albertazzi P, Sharma S. Urogenital effects of selective estrogen receptor modulators: a systematic review. Climacteric 2005; 8: 214-220.

59) Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, De Villiers TJ, Constantine GD, Chines AA. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo- and active-controlled clinical trial. J Bone Miner Res 2008; 23: 1923-1934.

60) Archer DF, Pinkerton JV, Utian WH, Menegoci JC, de Villiers TJ, Yuen CK, Levine AB, Chines AA, Constantine GD. Bazedoxifene, a selective estrogen receptor modulator: effects on the endometrium, ovaries, and breast from a randomized controlled trial in osteoporotic postmenopausal women. Menopause 2009; 16: 1109-1115.

61) Pickar JH, Komm BS. Selective estrogen receptor modulators and the combination therapy conjugated estrogens/bazedoxifene: A review of effects on the breast. Post Reprod Health 2015; 21: 112-121.

62) Palacios S, Currie H, Mikkola TS, Dragon E. Perspective on prescribing conjugated estrogens/bazedoxifene for estrogen-deficiency symptoms of menopause: a practical guide. Maturitas 2015; 80: 435-440.

63) Lev-Sagie A. Vulvar and vaginal atrophy: physiology, clinical presentation, and treatment considerations. Clin Obstet Gynecol 2015; 58: 476-491.

64) Hudita D, Posea C, Ceausu I, Rusu M. Efficacy and safety of oral tibolone 1.25 or 2.5 mg/day vs. placebo in postmenopausal women. Eur Rev Med Pharmacol Sci 2003; 7: 117-125.

65) Ricci G, Vitali M, Tambone V. Comment on: "The statistic evolution of the new Italian code of medical ethics". Eur Rev Med Pharmacol Sci 2016; 20: 2760-2761.

66) Cecchi R. Comment on: "The static evolution of the new Italian code of medical ethics". Eur Rev Med Pharmacol Sci 2016; 30: 2755-2757.

67) Falk SJ, Bober S. Vaginal Health During Breast Cancer Treatment. Curr Oncol Rep 2016; 18: 32.

68) Del Pup L, Salvagno F, Guido M, Giorda G, Vucetich A, Schettini S, Borini A, Peccatori F. Fertility and pregnancy after breast cancer treatment: evidence-based answers to the main questions that patients ask. WCRJ 2014; 1: e413.

69) Del Pup L, Borini A, Fisichella R, Peccatori F. Fertility preservation counseling of female cancer patients. WCRJ 2014; 1: e211.