OSPEMIFENE: AN ALTERNATIVE OPTION FOR THE TREATMENT OF VULVOVAGINAL ATROPHY

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INTRODUCTION

Vulvar and vaginal atrophy (VVA) is a chronic medical condition in women suffering from hypoestrogenism (Mac Bride et al 2010; Nappi et al 2017). The main sufferers of VVA are postmenopausal women which have a permanent reduced systemic oestrogen level (more than 50% of all postmenopausal women). A high prevalence of vaginal atrophy is also encountered in breast cancer survivors (23% to 61%) due to decreased circulating oestrogen levels related to breast cancer treatments. This permanent lack of oestrogenization of the vulvovaginal tissue in women suffering VVA leads to vaginal epithelium thinning and in turn may promote symptomatic vaginal infections and inflammations, as well as vaginal dryness, soreness, irritation and dyspareunia (Mac Bride et al 2010; Nappi et al 2017). These symptoms can cause emotional distress and reduced quality of life (Nappi et al 2017). Despite the high prevalence of women suffering from VVA this chronic condition is still heavily underdiagnosed and undertreated (Mac Bride et al 2010; Nappi et al 2017).

Currently available prescribed treatments for VVA include local oestrogen therapy (LET), systemic hormonal therapies (SHT), and systemic selective oestrogen receptor (ER) modulators (SERMS). Ospemifene is a SERM that recently became available in Europe for moderate to severe symptomatic VVA in post-menopausal women who are not candidates for local vaginal oestrogen therapy. As a SERM, ospemifene exerts its physiological effects by targeting the ER and modulating it differently in each tissue, that is as either an oestrogen antagonist (anti-oestrogenic effect) or an oestrogen agonist (oestrogenic effect) function in each tissue. Therefore, ospemifene binds to ER inducing a tissue specific effect that can differ to those effects induced by oestrogen in different tissues (Kangas and Unkila 2013; Mac Bride et al 2010; Nappi et al 2017).

EFFICACY OF OSPEMIFENE

Ospemifene efficacy for VVA treatment was proven by three double-blind, placebo controlled clinical studies: two 12 week Phase III efficacy studies (study 15-50310 and 15-50821) and a 52 week Phase III long-term safety study (study 15-50718) (**Table 1**). In all studies, a statistically significant change in vaginal maturation index (percentage of superficial and parabasal cells) and

OSPEMIFENE	
Efficacy	**Safety**
Improvement in: • Vaginal maturation index • Vaginal pH • Visual evaluation and atrophic findings* • Vaginal dryness • Vaginal and/or vulvar irritation/ itching • Vulvar pain and dyspareunia • Vulvar vestibular trophic score • Vaginal epithelium thickness • Stromal and epithelial oestrogen receptor expression • Overactive bladder syndrome • Urge urinary incontinence	Treatment emergent AEs (>3% incidence): • Hot flushes • Urinary tract infection • Headache • Nasopharyngitis • Muscle spasms • Vaginal discharge • Vulvovaginal candidiasis • Back pain • Sinusitis • Vulvovaginal mycotic infection
Contraindications	
• Unexplained genital bleeding • Signs/symptoms of endometrial hyperplasia • Active/past history of venous thromboembolic events • Known hypersensitivity to active substances/excipients • Patients with suspected breast cancer undergoing active treatment • Suspected/active sex-hormone dependent malignancy	
Candidates	
• Patients who have contraindications to local oestrogens - History of breast cancer - History of other hormone dependant cancers • Patients who suffer from porphyria • Patients who suffer from mild/moderate liver disease • Unable to administer LETs • Patients concerned about safety of hormone treatment • Patients concerned about side effects and cross-contamination to partner	
** petechiae, pallor, friability, vaginal dryness in the mucosa and vaginal redness in the mucosa*	

Table 1 - Efficacy, safety, contraindications and candidates for ospemifene

vaginal pH was observed from baseline to week 12 in the ospemifene 60 mg/ day group compared to the placebo control (P<0.0001). A statistical improvement was observed with ospemifene 60 mg/day treated patients at week 12 in each of the five parameters assessed in the vaginal visual evaluation (pete-

chiae, pallor, friability, vaginal dryness in the mucosa and vaginal redness in the mucosa). At 12 and 26 weeks, the proportion of patients with no atrophic findings for each of the five parameters was significantly greater in the ospemifene 60 mg/day group vs. the placebo group (P<0.0001). These improvements were maintained after one year of treatment where almost 80% of patients treated with ospemifene had no signs of vaginal atrophy vs. approximately 30% of patients who received placebo. A pooled analysis of these studies showed a significantly higher proportion of women which reported an improvement after 12 weeks of treatment with ospemifene in moderate/severe symptoms of vaginal dryness (ospemifene vs. placebo: 73% vs. 58%; P<0.00001), dyspareunia (76.7% vs. 63.9%; P<0.00001) and vaginal and/or vulvar irritation/itching (80.3% vs. 69.4%; P=0.0053) (Goldstein et al 2014; Nappi et al 2017). Additionally a study with 52 postmenopausal women suffering of vulvar pain and dyspareunia treated with ospemifene (60 mg/day) for 60 days showed a significant decrease from baseline in the mean scores for dryness (6.8 vs. 4.1, P=0.03), burning (7.5 vs. 2.8; P=0.01) and dyspareunia (9.0 vs. 5.4; P=0.001) and an additional reduction of vulvar vestibular trophic score (11.2 vs. 4.2; P≤0.002) and cotton swab test scores (2.81 vs. 1.25; P=0.001). The results confirmed the efficacy of ospemifene on postmenopausal vulvar vestibular symptoms and signs, and proved ospemifene to be effective in normalising vulvar vestibular innervation sensitivity (Murina et al 2018). Comparison of all these efficacy data with other studies involving vaginal oestrogens showed that the efficacy of ospemifene vs. placebo was comparable to, or better than, that seen in local oestrogens vs. placebo (Goldstein et al 2014; Nappi et al 2017).

Furthermore, efficacy of ospemifene was confirmed surgically in a study enrolling post-menopausal women undergoing surgical procedures. A total of 48 women were enrolled, 32 taking ospemifene between 28 to 77 days prior surgery and 16 placebo control women. The vaginal biopsies performed during surgery were histologically analysed and demonstrated that women previously treated with ospemifene had thicker vaginal epithelium (349 ± 64 vs. 245 ± 53 μm; P<0.001), higher proliferation index (212 ± 47 vs. 127 ± 28 Ki-67þ cells/mm; P<0.001), higher epithelial ER expression (27.3 ± 3.1 vs. 20.6 ± 2.9 point score; P<0.001) and stromal ER expression (26.6 ± 4.9 vs. 20.6 ± 2.6 point score; P<0.001) when compared to the control group. The authors concluded that one month ospemifene treatment was associated with an increased maturation and ER expression of the vaginal mucosa in postmenopausal women suffering from VVA (Alvisi et al 2017).

Moreover, two recent retrospective studies including postmenopausal women with VVA analysed the effectiveness of ospemifene in overactive bladder syndrome (OBS) and urge urinary incontinence (UUI) (Schiavi et al 2017, 2018a). Both retrospective studies showed an improvement from baseline in OBS and UUI after 12 weeks of ospemifene 60 mg/day treatment, with a reduction of urinary symptoms and five-fold reduction on mean number of voids in 24h (P<0.0001 both studies) as well as a 2-4 fold reduction in the Overactive Bladder questionnaire (P<0.001 both studies) (Schiavi et al 2017, 2018a).

Additionally, a decrease from baseline after 6 month ospemifene treatment was observed in another retrospective study in the mean number of positive urine cultures (12-fold decrease; P<0.0001) and dysuria (5-fold decrease; P<0.0001). These results indicate that ospemifene could be a valid alternative with excellent tolerability for urinary tract infection prevention in postmenopausal women (Schiavi et al 2018b).

SAFETY OF OSPEMIFENE

The most common treatment-related adverse events (TEAEs) of ospemifene in clinical trials were hot flushes (7.5% vs. 2.6% for ospemifene vs. placebo); vaginal discharge (3.7% vs. 0.3%) and headache (3.1% vs. 2.4%) (European Medicines Agency 2014a). Two recent post hoc studies which pooled safety data phase II and III double blinded placebo controlled studies established hot flushes as the most common TEAE (8.5% vs. 3.3% and 8.5% vs. 3.2%; P<0.0001 both studies), although their frequency decreased after 4 weeks of treatment (Schiavi et al 2017, 2018a, 2018b; Simon et al 2018). Additionally, a multivariable analysis showed that an increase in hot flushes was associated to prior hormone therapy (6 months before study) (P=0.0234), longer study treatment duration (P=0.0234), and more hot flush days per month at baseline (P=0.0313) (Constantine et al 2016). Furthermore, a recent placebo-controlled trial with postmenopausal women who were already experiencing existing moderate to very severe hot flushes did not show any worsening of these symptoms after 6-week ospemifene 60 mg/day treatment (Constantine et al 2016). Although hot flushes have been shown to be the most common TEAE responsible for treatment discontinuation, only 0.9% of the patients discontinued due to hot flushes, among other TEAEs that led to treatment discontinuation were headache (0.6%), nausea (0.4%), muscle spasms (0.4%) and vaginal discharge (0.4%) (Constantine et al 2016; European Medicines Agency 2014a; Simon et al 2018).

Additionally, caution is suggested for patients with active or past history of venous thromboembolic events (VTEs), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis and ospemifene should be issued on a case by case basis. While clinical studies have shown no increase in VTEs the risk of such events in ospemifene treated women could not be reliably estimated due to wide confidence intervals (European Medicines Agency 2014a). Furthermore, a post hoc analysis of phase II and III clinical trial data in postmenopausal women analysing lipid and coagulation parameters (cholesterol, high-density lipoproteins [HDL], low-density lipoproteins [LDL], triglycerides, etc.) showed that ospemifene did not have a detrimental effect even up to 12 months of use, while it significantly reduced total cholesterol at 6 months (-1.8% vs. 1.6% placebo; P=0.0345). At month 12 other reductions in triglycerides were also observed with significantly greater mean percent change (HDL: 2.3% vs -1.9%; LDL: -7.0% vs -2.1%; P<0.05) and VTE risk factors such as fibrinogen and protein C antigen levels were significantly improved (-8.7% vs 7.3% and -4.5% vs 6.6%; P<0.01) (Archer et al 2017).

OSPEMIFENE IN OTHER TISSUES

Ospemifene shows an oestrogenic impact in bone and vaginal tissues and a weak partial agonist/antagonist effects in the uterus (European Medicines Agency 2014b; Kangas and Unkila 2013).

Uterus tissue

Ospemifene shows a weak antagonist effect in the endometrium with a weak intrinsic agonistic property (Kangas and Unkila 2013; Nappi et al 2017). Ospemifene has proven to be safe for the endometrium in a Phase II/III clinical trial program in postmenopausal women with up to 52 weeks vs. placebo, where a four time increase was observed in the mean endometrial thickness from baseline to week 12 in the ospemifene group (0.4 mm ospemifene vs. 0.1 mm placebo) which slightly increased after 1 year of treatment (0.75 mm ospemifene vs. 0.17 mm placebo). No increased incidence of endometrium cancer or hyperplasia were observed (Kangas and Unkila 2013; Nappi et al 2017).

Bone tissue

The effects of ospemifene on bone turnover in postmenopausal women were examined in two Phase II placebo controlled trials (Kangas and Unkila 2013; Nappi et al 2017). Komi et al conducted a randomised, double-blind study with healthy postmenopausal women treated with ospemifene and raloxifene (SERM used in prevention and treatment of osteoporosis) where they measured biochemical markers of bone turnover (N- and C-terminal cross-linking telopeptides of type I collagen, bone-specific alkaline phosphatase, osteocalcin, procollagen type I N propeptide, and procollagen type I C propeptide in serum) at 3 months treatment and 2-4 weeks after cessation of medication. No significant differences among study groups were observed in the bone turnover resorption suggesting that ospemifene could have a bone protective effect in postmenopausal women. These findings were also observed in a randomised, placebo controlled study by Komi et al, which demonstrated that ospemifene is effective in reducing bone turnover in postmenopausal women (Kangas and Unkila 2013; Nappi et al 2017).

Breast tissue

Due to the high incidence of breast cancer survivals which suffer from VVA, the study of ospemifene in breast tissue is of great interest. Ospemifene's effect in breast tissue is antagonistic and anti-proliferating (European Medicines Agency 2014b; Kangas and Unkila 2013; Nappi et al 2017). An analysis using ex vivo explant cultures showed an inhibitory effect on mammary tissue similar to that of other SERMS such as raloxifene and tamoxifen. The investigation of ospemifene in regards to its effect in breast tissue in a clinical setting is still preliminary as, although no increase in breast tumours have been observed in the clinical trials performed, the follow-up periods of these trials have been too short in order to fully evaluate ospemifene's long term effect (European Medicines Agency 2014b; Kangas and Unkila 2013; Nappi et al 2017). Nevertheless, three of the clinical studies which were conducted to evaluate the overall safety of ospemifene included mammograms to assess breast safety. In total, only two cases

of breast cancer were reported in the placebo groups of the clinical trials and no cases were reported in the ospemifene groups (Nappi et al 2017). A recent post hoc analysis of pooled safety data from six phase II and III double blinded placebo controlled studies showed that breast cancer and other breast related TEAE incidences were comparable between ospemifene (2.5%) and placebo (2.2%) (Simon et al 2018). Additionally, the safety of using ospemifene concomitantly with oestrogens or other SERMs, such as tamoxifen (indicated for breast cancer patients) has not been studied and its concurrent use is not recommended. Therefore, ospemifene should be used for the treatment of VVA only after the treatment of breast cancer, including adjuvant therapy, has been completed.

Cervical tissue

Survivors of other hormone based cancers such as cervical cancer (CC) can have a worsened quality of life and sexual function after their cancer treatment. A single arm prospective study which included CC survivors diagnosed with VVA showed a significant improvement after 6 months of treatment (compared to baseline) for the patients' vaginal health index (10 vs. 16 points; $P<0.001$), sexual function and quality of life (50 vs. 58 points; $P=0.01$) (De Rosa et al 2017). This suggests that ospemifene may be suitable for the treatment of VVA in CC survivors.

CONCLUSIONS

Women with VVA have a greater risk of genitourinary conditions compared to those without. Lack of information and the fact that many women do not seek consultation for VVA symptoms are two of the facts that make VVA an underreported and underdiagnosed condition. Ospemifene is a SERM that has reiteratively proven to be effective in VVA women with dyspareunia, showing an increase in vaginal maturation index, improvement in vaginal pH and decrease in prevalence of atrophic findings. Ospemifene treated women have reported improved symptoms such as vaginal dryness, dyspareunia and vaginal and/or vulvar irritation/itching. Moreover, ospemifene has shown to improve vulvar vestibular symptoms and even shown to be effective in normalising vulvar vestibular innervation sensitivity. Studies evaluating the safety of treatment for up to a year have shown that ospemifene is safe with a low discontinuation due to TEAEs and lack of detrimental effects on the breast, cervical and bone tissues. Furthermore, mean endometrial thickness was documented to increase after 1 year treatment with no increased incidence of endometrium cancer or hyperplasia. Additionally, ospemifene has been shown to be as effective as raloxifene in reducing bone turnover in postmenopausal women.

However, despite the comparable efficacy of ospemifene vs. placebo to oestrogen vs. placebo, ospemifene is currently indicated for women who are not candidates for LET and it is up to the gynaecologist to make an appropriate therapeutic decision. Studies whereby ospemifene is directly compared to vaginal and systemic oestrogens are therefore required to modulate the current indication.

References

- Alvisi, S., Baldassarre, M., Martelli, V., Gava, G., Seracchioli, R., and Meriggiola, M.C. (2017). Effects of ospemifene on vaginal epithelium of post-menopausal women. Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol. 33, 946–950.
- Archer, D.F., Altomare, C., Jiang, W., and Cort, S. (2017). Ospemifene's effects on lipids and coagulation factors: a post hoc analysis of phase 2 and 3 clinical trial data. Menopause N. Y. N 24, 1167–1174.
- Constantine, G.D., Archer, D.F., Pollycove, R., Jiang, W., Altomare, C., and Pinkerton, J.V. (2016). Ospemifene's effect on vasomotor symptoms: a post hoc analysis of phase 2 and 3 clinical data. Menopause N. Y. N 23, 957–964.
- De Rosa, N., Lavitola, G., Giampaolino, P., Morra, I., Nappi, C., and Bifulco, G. (2017). Impact of Ospemifene on Quality of Life and Sexual Function in Young Survivors of Cervical Cancer: A Prospective Study. BioMed Res. Int. 2017, 7513610.
- European Medicines Agency (2014a). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/002780/WC500182777.pdf.
- European Medicines Agency (2014b). http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_Initial_authorisation/human/002780/WC500177633.pdf.
- Goldstein, S.R., Bachmann, G.A., Koninckx, P.R., Lin, V.H., Portman, D.J., Ylikorkala, O., and Ospemifene Study Group (2014). Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. Climacteric J. Int. Menopause Soc. 17, 173–182.
- Kangas, L., and Unkila, M. (2013). Tissue selectivity of ospemifene: pharmacologic profile and clinical implications. Steroids 78, 1273–1280.
- Mac Bride, M.B., Rhodes, D.J., and Shuster, L.T. (2010). Vulvovaginal atrophy. Mayo Clin. Proc. 85, 87–94.
- Murina, F., Di Francesco, S., and Oneda, S. (2018). Vulvar vestibular effects of ospemifene: a pilot study. Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol. 1–5.
- Nappi, R.E., Murina, F., Perrone, G., Villa, P., and Biglia, N. (2017). Clinical profile of women with vulvar and vaginal atrophy who are not candidates for local vaginal estrogen therapy. Minerva Ginecol. 69, 370–380.
- Schiavi, M.C., Zullo, M.A., Faiano, P., D'Oria, O., Prata, G., Colagiovanni, V., Giannini, A., Di Tucci, C., Perniola, G., Di Donato, V., et al. (2017). Retrospective analysis in 46 women with vulvovaginal atrophy treated with ospemifene for 12 weeks: improvement in overactive bladder symptoms. Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol. 33, 942–945.
- Schiavi, M.C., Sciuga, V., Giannini, A., Vena, F., D'oria, O., Prata, G., Di Tucci, C., Savone, D., Aleksa, N., Capone, C., et al. (2018a). Overactive bladder syndrome treatment with ospemifene in menopausal patients with vulvovaginal atrophy: improvement of sexuality? Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol. 1–4.
- Schiavi, M.C., Di Pinto, A., Sciuga, V., Faiano, P., Di Tucci, C., D'oria, O., Martoccia, A., Prata, G., Carraro, C., Ostuni, R., et al. (2018b). Prevention of recurrent lower urinary tract infections in postmenopausal women with genitourinary syndrome: outcome after 6 months of treatment with ospemifene. Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol. 34, 140–143.
- Simon, J.A., Altomare, C., Cort, S., Jiang, W., and Pinkerton, J.V. (2018). Overall Safety of Ospemifene in Postmenopausal Women from Placebo-Controlled Phase 2 and 3 Trials. J. Womens Health 2002 27, 14–23.

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PATOLOGIE GINECOLOGICHE BENIGNE E DOLORE:

come scegliere il meglio fra terapie mediche e chirurgiche

MILANO
25 MAGGIO 2018

ATTI E APPROFONDIMENTI DI FARMACOLOGIA

a cura di Alessandra Graziottin

PROGRAMMA

8.00 - 8.45 Registrazione

8.45 - 9.00 Apertura dei lavori

Lettura magistrale

9.00 - 9.30 **L'adolescente con dolore ginecologico: quando la prima scelta è la terapia medica**
Vincenzina Bruni (Firenze)
Introducono: Alessandra Graziottin (Milano) e Vincenzo Stanghellini (Bologna)

09.30 11.00 Il dolore mestruale e pelvico nella donna giovane: la prospettiva chirurgica

Moderatori: Filippo Murina (Milano) e Rodolfo Sirito (Genova)

9.30-9.50 **Neuroanatomia pelvica e implicazioni chirurgiche**
Marcello Ceccaroni (Verona)

9.50-10.10 **Dolore pelvico nell'adolescente: quando la prima scelta è chirurgica**
Mario Meroni (Milano)

10.10-10.30 **I trigger anorettali del dolore pelvico**
Aldo Infantino (Pordenone)

10.30-10.45 **Discussione**

10.45-11.00 **Coffee Break**

Letture magistrali

11.00 12.00

11.00-11.30 **Cervello viscerale e dolore: il ruolo dell'intestino**
Vincenzo Stanghellini (Bologna)
Introducono: Alessandra Graziottin (Milano) e Riccardo Torta (Torino)

11.30-12.00 **Lettura magistrale**

Endometriosi: il punto sul dolore e gli errori da non commettere
Edgardo Somigliana (Milano)
Introducono: Vincenzina Bruni (Firenze) e Mario Meroni (Milano)

12.00 13.15 Endometriosi e dolore: come scegliere fra terapia medica e terapia chirurgica

Moderatori: Alessandra Graziottin (Milano) e Aldo Infantino (Pordenone)

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Stefano Luisi (Siena)

12.20-12.40 **Prevenzione delle complicanze nella chirurgia per endometriosi**
Marcello Ceccaroni (Verona)

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PROGRAMMA

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Lettura magistrale

14.00
14.30

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Introducono: Alessandra Kustermann (Milano) e Stefano Luisi (Siena)

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15.40

Fibromi uterini: strategie di personalizzazione terapeutica

Moderatori: Franca Fruzzetti (Pisa) e Alessandra Graziottin (Milano)

14.30-14.50 **Fibromi uterini e infertilità**
Alessandro Fasciani (Genova)

14.50-15.10 **Fibromatosi uterina: ruolo della miolisi in radiofrequenza**
Rodolfo Sirito (Genova)

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Alessandra Graziottin (Milano)

15.30-15.40 **Discussione**

15.40
18.00

Il dolore pelvico, vulvare e vaginale: prospettive terapeutiche

Moderatori: Alessandra Graziottin (Milano), Filippo Murina (Milano) e Vincenzo Stanghellini (Bologna)

15.40-16.00 **Dolore pelvico neuropatico, tra sistema nervoso centrale e cervello viscerale: quali terapie farmacologiche?**
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Filippo Murina (Milano)

16.20-16.40 **Dolore vulvo-vaginale, atrofia vulvo-vaginale e comorbilità sessuali, proctologiche, vescicali, sistemiche: terapie farmacologiche su indicazioni del Progetto Vu-Net**
Alessandra Graziottin (Milano)

16.40-17.00 **Dolore vulvare e disfunzione del pavimento pelvico: dalla semeiotica alle scelte fisioterapiche**
Arianna Bortolami (Padova)

17.00-17.30 **Discussione plenaria**

17.30-18.00 **Conclusioni**
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18.00 **Test ECM**

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