THERAPEUTIC AGENTS: ARE THEY SAFE?

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TREATMENTS FOR VVA/DYS Pareunia

• Systemic HT/ET
• Local ET
• Ospemifene

I will NOT discuss systemic HT/ET (it would take the entire lecture)

Local Estrogen Therapy

LET’S START WITH THE LABELLING… (AND REMEMBER WE ARE TALKING ABOUT LOCAL E2)

Boxed Warning (Class Labeling for all Estrogens regardless of dose or route of administration)

• Estrogens increase the risk of endometrial cancer
• Should not be used for prevention of cardiovascular disease or dementia
• ↑ Risk of stroke and DVT
• E+P in WHI ↑Risk of MI, stroke, invasive breast cancer, PE and DVT
Boxed Warning (Class Labeling for all Estrogens regardless of dose or route of administration)

- ↑ risk of “developing probable dementia in PM women >65 y/o” in WHIMS sub study (Women’s Health Initiative Memory Study)
- Restates “lowest effective doses and shortest-duration consistent with treatment goals and risks for individual women”

Contraindications (Estrogen Class Labeling regardless of dose or route of administration)

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active deep vein thrombosis, pulmonary embolism or a history of these conditions

Concerning Breast Cancer...

- ALL estrogen containing products’ package inserts clearly state that these products are “contraindicated in women with estrogen dependent neoplasias including breast cancer”
- Thus ALL such use (remember we are on LOCAL Rx) would be “off label” and against FDA recommendations.

DVT, Dementia, MI, Stroke

- As already mentioned ALL Estrogen products contain these warnings.
- Obviously these (as well as breast cancer) when discussing LOCAL use should depend on level of systemic absorption (if any) AND, if present, its clinical relevance.

SYSTEMIC ABSORPTION

- Absorption of vaginal estrogen depends primarily upon the estrogen dose (e.g. Estring® vs. FemRing®)
- Severity of vaginal atrophy may have an effect on systemic absorption
- Some studies report systemic absorption is highest in the first days or weeks of therapy and then decreases with ongoing treatment

SYSTEMIC ABSORPTION

- Another study using highly sensitive E₂ measurements did not support this finding.
- One hypothesis is that the thin atrophic vaginal epithelium allows initial higher absorption which diminishes as epithelium thickens with treatment.

PROBLEMS WITH SUCH DATA

- Each set of information is collected in a different study on different individuals.
- Each study has different sample sizes, estrogen-measurement techniques, schedules, and reference ranges.
- Does not include CEE (Conjugated Equine Estrogen) because CEE contains several estrogenic compounds that are NOT typically measured in assays for estradiol.

SO WHAT ABOUT CEE CREAM?

- Approved for TWO indications each with DIFFERENT dosing.
- For “atrophic vaginitis and Kraurosis Vulvae”
- 21 days of 0.5 gm intravaginally daily and then 7 days off. “Adjust dose (0.5-2.0 gm) based on individual response”

SO WHAT ABOUT CEE CREAM?

- For “moderate to severe dyspareunia, a symptom of VVA due to menopause”.
- 0.5 gm. intravaginally twice weekly OR cyclical regimen of 21 days on and 7 days off.
What Do the Data show: CEE Cream

- Each gram of cream contains 0.625 mg CEE
- 24 weeks of 2gm/day resulted in 47% of women having Estradiol levels ABOVE a menopausal range.
- ¼ gm of CEE cream T.I.W for 6 months showed no significant increase in plasma levels of E2 in 20 women.

TAKE HOME MESSAGE: ABSORPTION

- Appears to be less with tablets and local ring than creams.
- Little good data to truly rely on (different dosing, assays, study populations, etc.)

What Do the Data Show: Breast Cancer Recurrence

- A prospective cohort study of 1472 women with breast cancer included 69 treated for an average of one year with local E2 (range 0.1-5 years) with no ↑ risk of recurrence


What Do the Data Show: Breast Cancer Risk

- In a prospective observational study of 18,314 women, local vaginal estrogen therapy was not associated with an increased risk of breast cancer.


What Do the Data Show: Aromatase Inhibitors

- AIs, by blocking estrogen synthesis, result in circulating E2 levels < 1 pg/ml
- Limited data with estrogen coadministration
- One study (25-ug E2 tablets) resulted in increases from baseline (0.82 pg/ml) to day 14 (19.6 pg/ml) but by day 28 all levels were < 10pg/ml

TAKE HOME MESSAGE: BREAST

No good level I evidence FOR or AGAINST safety of local E2 in women WITH or WITHOUT a history of breast cancer but CLEARLY less absorption than systemic E2.

NAMS 2013 Position Statement Recommendation

“For women with a history of breast or endometrial cancer, management depends upon a woman’s preference, need, understanding of potential risks, and consultation with her oncologist.”

ENDOMETRIAL SAFETY

A primary concern of use of any estrogen therapy in women with an intact uterus is the risk of endometrial hyperplasia and even occasionally carcinoma associated with unopposed estrogen.

ENDOMETRIAL SAFETY

Although available evidence suggests that low doses of locally administered vaginal estrogen are generally safe in the endometrium, the data are limited.

ENDOMETRIAL SAFETY


ENDOMETRIAL SAFETY (SINCE COCHRANE REVIEW)

- 10-ugr E2 tablet in 336 PM women with a uterus had no ↑ in EM proliferation or hyperplasia. ¹
- Another study of 10-ugr E2 tablet (n-205) reported a single case of Stage II EM carcinoma considered unlikely to have developed in response to the relatively short course of study drug exposure. ²

¹ Ulrich L Climacteric 2010, 13(3):228-237
TAKE HOME MESSAGE: ENDOMETRIUM

- Progestogen is generally not indicated when low-dose vaginal estrogen is administered for symptomatic VVA. Endometrial safety data are not available for use greater than one year.

TAKE HOME MESSAGE: ENDOMETRIUM

- If a woman is at high risk for endometrial cancer, OR is using a higher dose of vaginal ET OR is using vaginal ET for more than 1 year, transvaginal ultrasound or intermittent progestogen therapy may be considered. There are insufficient data to recommend routine annual endometrial surveillance in asymptomatic women using vaginal ET.

TAKE HOME MESSAGE: ENDOMETRIUM

- Spotting or bleeding in any postmenopausal woman who has an intact uterus (local E2 therapy or not) requires a thorough evaluation, which may include transvaginal ultrasound and/or endometrial biopsy.

BUT KEEP IN MIND...ACOG PRACTICE BULLETIN 7/2012

“Blind EM biopsy is only an endpoint when it reveals cancer or atypical complex hyperplasia.”

( Maybe I can talk on that NEXT year?)

WHAT ABOUT... OSPEMIFENE

VTE
WHAT THE LABELLING SAYS:

- “Contraindications: Active deep vein thrombosis (DVT), pulmonary embolism (PE), or a history of these conditions”

WHAT THE DATA SHOW:

- Incidence of VTE in the clinical trials was 1.45/1000 women-years with Ospemifene vs. 1.04/1000 women-years with Placebo

WHAT IS THE TAKE HOME MESSAGE?

- VTE risk in the background population is about 1/1000 women/year.
- With systemic Estrogen, Tamoxifen, Raloxifene (and I believe Ospemifene) it increases to 2.5/1000 women/year. These are all “estrogens” in the venous system. I do not believe Ospemifene is any less thrombogenic.

Breast Cancer

WHAT THE LABELLING SAYS:

- “Osphena™ has not been adequately studied with breast cancer therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.”

WHAT THE DATA SHOW:

- In all the Ospemifene trials there were 2 cases of invasive breast cancer (one placebo, one Ospemifene)
- Abundant data point to an antiestrogen effect in preclinical models of breast cancer. (MCF-7 and other cell lines of estrogen dependent breast cancer)
WHAT IS THE TAKE HOME MESSAGE?

• All SERMs have antiestrogenic effects in preclinical models of breast cancer. Thus, Ospemifene will certainly have a positive SERM like effect on breast tissue. However the magnitude of that effect with this dosage is totally unknown and unstudied. Thus substitution of Ospemifene for other SERMs studied and approved for their effect on breast would be ill advised.

WHAT IS THE TAKE HOME MESSAGE?

• In my opinion, the patient with an old history of breast cancer who has finished her Tamoxifen or Aromatase Inhibitor, now with a new partner who has dyspareunia from VVA is EXACTLY the kind of patient who would benefit MOST from Ospemifene

UTERINE EFFECTS

WHAT THE LABELLING SAYS:

• “In the endometrium, Osphena™ has estrogenic agonistic effects. There is an increased risk of endometrial cancer in a woman who uses unopposed estrogen.”

WHAT THE DATA SHOW:

• In all women treated with Ospemifene for 52 weeks there were no cases of endometrial cancer.
• There was one case of simple endometrial hyperplasia without atypia

WHAT THE DATA SHOW: (THE SINGLE CASE OF SIMPLE HYPERPLASIA)

• 54 year old woman, menopausal at 49. 2 years of HT. On Ospemifene 4 months. Episode of staining. Bx showed active proliferation. Study drug stopped. No treatment given. Plan to follow up at 3 months. At 88 days, bled again. Bx showed simple hyperplasia without atypia. Treated with a single course of progestin. D&C revealed benign polyp and inactive EM.
WHAT THE LABELLING SAYS:

- “The incidence of any type of proliferative endometrium (weakly proliferative plus active plus disordered) was 86.1 per 1000 in Osphena vs. 13.3 per 1000 placebo.”

WHAT THE DATA SHOW:

- At 52 weeks the incidence of simple hyperplasia with ospemifene was 0.3% and active proliferation was 1.0%.

HISTOLOGY 101

- Active proliferation is characterized by abundant mitotic activity and glandular progression.
Inactive/atrophic EM is characterized by simple tubular glands which lack mitotic activity and fibrotic stroma with increased collagen fibers.

“Weakly proliferative” is a misnomer which is confusing to clinicians and apparently to the FDA as well.

Histologically it appears as inactive endometrium with rare mitotic figures and no glandular progression.
“Weakly” proliferative is much closer to inactive/atrophic EM and should be considered a variant of those and not combined with active.

THE UTERINE SAFETY STUDY WITH RALOXIFENE

STUDY DESIGN

- 12 Month prospective, double blind, randomized
- 415 women, 2-8 years postmenopausal ranging in age from 47-60

Treatment Arms:
- Placebo (n=109)
- Rlx 60mg/day (n=101)
- Rlx 150mg/day (n=105)
- Conjugated Equine Estrogen 0.625 mg/day (n=100)

FURTHERMORE

A 12-Month Comparative Study of Raloxifene, Estrogen, and Placebo on the Postmenopausal Endometrium

STEVEN B. COLOSFONE, MD; WAIN H. SIEGEL, MD; BRENNAN E. RAJACOPOLAY, PHD; JENNIFER L. WILKIE; BRIAN W. WALKER, MD; AND ANNA K. PARSONS, MD
HISTOLOGY RESULTS

At Endpoint

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<td>39%</td>
<td>2%</td>
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YOU DECIDE…`

• Is ospemifene more like raloxifene in the endometrium
  (1% active proliferation, 0.3 simple hyperplasia vs. 3% active proliferation, 0% hyperplasia for raloxifene, at one year)

YOU DECIDE…

• More like unopposed estrogen (39% active estrogen, 23% hyperplasia, at one year or less if they bled)

OR

I acknowledge that ospemifene does not have the weight of a study like the MORE Trial (3955 women treated for 3 years with Raloxifene who showed a 20% non significant reduction in EM cancer)…

…but to call Ospemifene “estrogenic” in the uterus (causing The Medical Letter to recommend progestogen), in my opinion, is unfair to patients and clinicians as well.
WHAT IS NOT IN THE LABEL (THAT SHOULD BE...)

In the 52 week trial the incidence of any vaginal bleeding (which in clinical practice mandates evaluation) was 1.4% (5 pts.) 4 had inactive EM, 1 had active proliferation.

Thus in clinical practice you can expect that 1 in 70 patients placed on Ospemifene will experience bleeding.
And of those who bleed 4/5 will have inactive, atrophic EM and 1/5 of those will have active proliferation.

Thus, in my opinion, absent bleeding, in ospemifene patients no periodic surveillance nor progestin therapy is warranted.

IN SUMMARY

VVA is a serious medical concern with important medical and quality of life issues.
Safety is a huge concern especially when a condition like VVA is not “life threatening”.

Local estrogens are labeled for increasing VTE although data suggesting that are few.
Local estrogens have minimal effect on EM, and although long term data is lacking, routine use of progestogen is unnecessary.
Local estrogens are minimally absorbed systemically (if at all) and are likely safe in patients with an old history of breast cancer although Level 1 Evidence is lacking.
IN SUMMARY
- Ospemifene is a SERM that is used systemically
- Ospemifene is estrogenic in the venous system
- Ospemifene, in preclinical use, is an antiestrogen in breast. The MAGNITUDE of that effect in women is unknown

THANK YOU FOR YOUR ATTENTION!

IN SUMMARY
- Although Ospemifene is labelled as estrogenic in the EM, studies place it much more like Raloxifene in the uterus than it is like estrogen in the uterus
- The incidence of vaginal bleeding with Ospemifene is 1.4% but 4/5 of those are inactive EM while only 1/5 of those are actively proliferative