Novel Oral, Continuous-combined Solubilized 17β-Estradiol and Natural Micronized and Suspended Progesterone Provided Endometrial Protection: Comparison of 2 Randomized Controlled Trials

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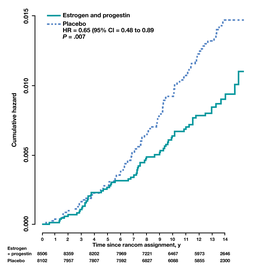
Introduction

- Is the incidence of endometrial cancer different between medroxyprogesterone acetate (MPA) and natural progesterone (P4) when used with estrogens for endometrial protection?
- The Women's Health Initiative (WHI) was a randomized, double-blind, placebo-controlled trial, which evaluated the effect of 0.625 mg conjugated equine estrogen (CEE) plus 2.5 mg MPA daily vs placebo on the endometrium[1]
  - 16,608 postmenopausal women with an intact uterus received treatment for a median of 5.6 years
  - 12,788 consented for follow-up study and were followed for a median of 13 years
- The WHI reported a lower incidence of endometrial cancer with daily 0.625 mg CEE/2.5 mg MPA than with placebo after 13 years of cumulative follow-up **(Figure 1)**[1]
  - CEE/MPA vs Placebo: 66 vs 95 case patients
  - HR 0.65; 95% CI, 0.48–0.89 (*P*=0.007)

Figure 1. Kaplan-Meier Estimates of Cumulative Hazards of Endometrial Cancer in the WHI[1]



- The Women's Health, Osteoporosis, Progestin, Estrogen (Women's HOPE) study also showed that MPA prevented endometrial hyperplasia with various CEE doses[2]

Can Progesterone Also Protect the Endometrium?

- The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial showed that 200 mg of cyclic P4 with 0.625 mg CEE (dosed separately) protected the endometrium from hyperplasia[3]
  - Incidence of hyperplasia with CEE/cyclic P4 similar to that with placebo
- The REPLENISH trial showed for the first time in a large, randomized, controlled trial that TX-001HR, the combination of continuously combined 17β-estradiol (E2) with P4, resulted in no cases of endometrial hyperplasia or endometrial malignancy after 1 year
  - TX-004HR (TherapeuticsMD, Boca Raton, FL) is an investigational vaginal E2 drug not yet approved by the U.S. FDA

Objective

- To compare the separately conducted REPLENISH (E2/P4) and Women's HOPE (CEE/MPA) trials with regard to endometrial protection and uterine bleeding

Study Design

Women's HOPE Study[2]

- 12-month randomized, double-blind, placebo-controlled, multicenter trial in menopausal women with an intact uterus
- Evaluated the endometrial safety and uterine bleeding of doses of continuous combined CEE and MPA or CEE alone vs placebo for 1 year
  - CEE doses: 0.625 mg, 0.45 mg, 0.3 mg
  - CEE/MPA doses: 0.625/2.5 mg, 0.45/2.5 mg, 0.45/1.5 mg, 0.3/1.5 mg

REPLENISH Trial[5]

- 12-month, randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in menopausal women with an intact uterus (NCT01942668)
  - TX-001HR is an investigational combination of solubilized E2 and micronized and suspended P4 in a single, oral, softgel capsule
  - Currently being evaluated for the treatment of moderate-to-severe vasomotor symptoms in menopausal women with an intact uterus
- Evaluated endometrial safety and uterine bleeding of continuous combined doses of TX-001HR vs placebo to treat moderate-to-severe vasomotor symptoms
  - E2/P4 doses: 1/100 mg, 0.5/100 mg, 0.5/50 mg, 0.25/50 mg

Endometrial Hyperplasia Assessment[2,6]

- Endometrial biopsies were performed and evaluated similarly in both studies
- Incidence of endometrial hyperplasia at year 1 was a primary endpoint of both trials
  - FDA guidance: ≤1% hyperplasia rate; upper bound of the one-sided 95% CI ≤4%
- Endometrial biopsies were performed at baseline and Month 12/end of treatment (as well as cycle 6 in the Women's HOPE Study)
- Biopsy specimens were processed by a central laboratory
  - Biopsy slides were reviewed by 2 or 3 pathologists
  - A consensus read of 2 of the 3 pathologists was required to diagnose endometrial hyperplasia
  - No hyperplasia on biopsy at baseline for study eligibility
- Any patient who developed endometrial hyperplasia was withdrawn from the study and given the appropriate treatment

Bleeding and Spotting Assessment[5,7]

- Women in both studies completed diaries of daily vaginal bleeding and spotting up to month 12
  - Bleeding: required sanitary protection
  - Spotting: did not require sanitary protection
- Bleeding profiles, including cumulative amenorrhea (no bleeding or spotting) were assessed between treatment groups over thirteen 28-day cycles

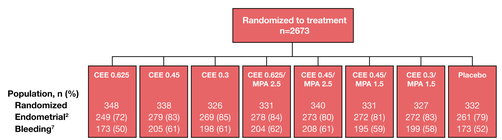
Results

Disposition and Demographics

Women's HOPE Study[2,7,8]

- Women had a mean age of 53 years, and mean BMI of 24 kg/m^2
- Majority was white (88%), followed by African American (6%) or Hispanic (4%)
- 19% of women discontinued the study

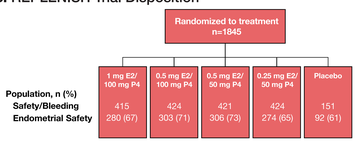
Figure 2. Women's HOPE Study Disposition



REPLENISH Trial[5]

- Women had a mean age of 55 years (40–66), and mean BMI of 27 kg/m^2
- 65% were white and 32% were African American
- 69% of women completed the study at 52 weeks

Figure 3. REPLENISH Trial Disposition[5]



Endometrial Safety

Women's HOPE Study with CEE/MPA[2]

- Endometrial hyperplasia incidence ranged from 0 to 0.37% with CEE/MPA after 1 year (**Table 1**)
  - Addition of MPA prevented the endometrial hyperplasia observed in women treated with CEE alone

Table 1. Endometrial Hyperplasia Incidence in the Women's Hope Study

Treatment (mg)	n	Total No. of Hyperplasia	Hyperplasia Rate, %	95% CI
CEE 0.625/MPA 2.5	278	0	**0**	0.00–1.32
CEE 0.45/MPA 2.5	273	0	**0**	0.00–1.34
CEE 0.45/MPA 1.5	272	1	**0.37**	0.01–2.03
CEE 0.3/MPA 1.5	272	1	**0.37**	0.01–2.03
Placebo	261	0	**0**	0.00–1.40

CEE: Conjugated equine estrogens; MPA: medroxyprogesterone acetate.

REPLENISH Trial with E2/P4[5]

- Endometrial hyperplasia incidence was 0% after 1 year (**Table 2**)
- No endometrial malignancies detected with any TX-001HR dose or placebo

Table 2. Endometrial Hyperplasia Incidence in the REPLENISH Trial

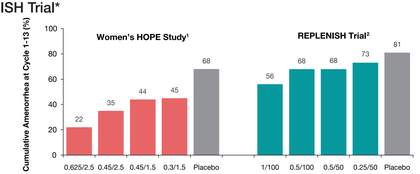
Treatment (mg)	n	Total No. of Hyperplasia	Hyperplasia Rate, %	1-sided upper 95% CI
E2 1 /P4 100	280	0	**0**	1.06%
E2 0.5 /P4 100	303	0	**0**	0.98%
E2 0.5 /P4 50	306	0	**0**	0.97%
E2 0.25 /P4 50	274	0	**0**	1.09%
Placebo	92	0	**0**	3.20%

E2: 17βestradiol; P4: progesterone.

Cumulative Amenorrhea

- In the Women's HOPE Study, cumulative amenorrhea from cycles 1–13 was significantly lower with CEE/MPA (22–45%) than with placebo (68%; **Figure 4**)[7]
  - Increased over time
  - All lower-dose CEE/MPA had significantly higher cumulative amenorrhea than 0.625/2.5 in cycles 1–13 and 7–13
  - By cycle 13, it ranged from 76% to 89% with CEE/MPA vs 96% with placebo
- In the REPLENISH Trial, cumulative amenorrhea from cycle 1 to 13 was high with TX-001HR (56–73%), but lower than with placebo (81%; **Figure 4**)[5]
  - Increased over time
  - >90% had amenorrhea during cycle 13

Figure 4. Cumulative Amenorrhea from Cycle 1 to 13 in the Women's HOPE Study and the REPLENISH Trial*



*CEE/MPA and E2/P4 doses were not directly compared in a head-to-head study

Conclusions

- TX-001HR (E2/P4) provided endometrial protection in the 1-year REPLENISH trial
  - Incidence rates of endometrial hyperplasia at 1 year with all P4 doses continuously combined with estradiol, were 0%
  - No cases of endometrial cancer were observed
  - Cumulative amenorrhea rates increased over time. At 12 months:
    - Rates were 56–73% with E2/P4 vs 81% with placebo
- If approved, TX-001HR may be an appropriate alternative combination hormone therapy for treating moderate-to-severe vasomotor symptoms, while protecting the endometrium

References

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Disclosures

JHP is a consultant for Pfizer, Shionogi Inc, and TherapeuticsMD (stock options). BB and SM are employees of TherapeuticsMD (with stock/stock options). BB is also on the Board of TherapeuticsMD. TherapeuticsMD supported the medical writing assistance provided by Dominique Verlaan, PhD, CMPP (Precise Publications, LLC).

Presented at the 2018 ENDO Meeting, March 17-20, 2018 in Chicago, IL