Correlations of Serum Estradiol and Estrone Concentrations with Menopausal Outcomes and Bleeding

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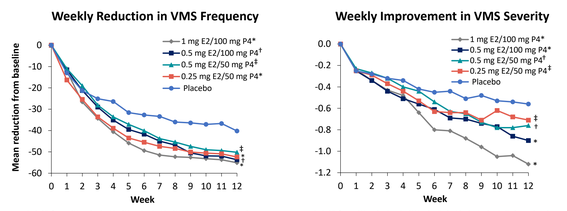
Introduction

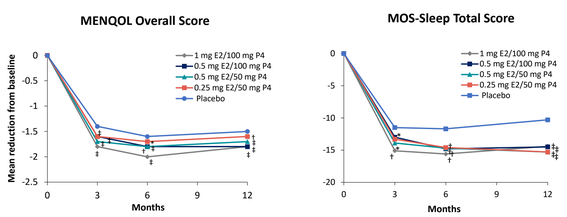
- The occurrence of vasomotor symptoms (VMS) with estrogen deficiency at menopause is well established. VMS in postmenopausal women are effectively treated with estrogen-progestogen therapy, which reduces both frequency and severity of these symptoms. Such reductions in VMS frequency may lead to improvements in quality of life and sleep outcomes for postmenopausal women.[1]
- In the 12-month REPLENISH trial that evaluated 4 doses of TX-001HR (TherapeuticsMD, Boca Raton, FL), an investigational, once-daily, oral capsule containing 17β-estradiol (E2) and progesterone (P4), most doses significantly reduced the frequency and severity of moderate to severe VMS,[2] and significantly improved quality of life (Menopause-specific Quality of Life [MENQOL])[3] and sleep outcomes (Medical Outcomes Study [MOS]-Sleep scale)[4] scores (**Figure 1**)
- How systemic estrogen levels correlate with outcome improvement or irregular bleeding in postmenopausal women is not known

Figure 1. Improved Clinical Outcomes with E2/P4 in the REPLENISH Trial



P<0.05 from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6-12 vs placebo.

P<0.05 from *Weeks 3–12; †Weeks 7, 9–12; ‡Weeks 6, 7, 9 vs placebo.



*P<0.05; †P<0.01; ‡P<0.001 vs placebo.

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Objective

To investigate the correlations between serum concentrations of estradiol (E2) and estrone (E1) and clinical outcomes before and during hormone therapy in the REPLENISH trial

Methods

- A large cohort of postmenopausal women (aged 40-65 with a uterus) seeking treatment for VMS were randomized to daily E2/P4 (mg/mg) 1/100, 0.5/100, 0.5/50, 0.25/50 or placebo (VMS substudy, n=726), while the remainder were randomized to the active doses only for endometrial safety, in the REPLENISH trial (NCT01942668)
- Serum E2 and E1 concentrations were measured at baseline and at various time points, including week 12, using gas chromatography and tandem mass spectrometry
- Clinical outcomes collected at various time points included changes in frequency and severity of VMS and days with vaginal bleeding or spotting (from daily diary data), as well as the questionnaires for MENQOL and MOS-Sleep scale scores
- Correlations and predictions were obtained using correlation analysis and logistic regression
  - Analyses were performed on all treatment groups combined in the modified intention-to-treat population (randomized women who took at least one study dose)
  - Correlation analysis computed the correlation coefficient (r) indicating the strength of the relationship, as well as a *P*-value
  - Logistic regression generated odds ratios (OR) of bleeding/spotting ≥4 days/week with respect to increases in serum E2 and E1 concentrations
  - A common logarithmic transformation of serum hormone concentrations and frequency and severity of hot flushes was performed to resolve the skewness of the data distribution

Results

Disposition and Demographics

- Of the 1835 women who took the study medication (safety population), 1833 were eligible for the MITT population (n=1682 for TX-001HR doses; n=151 for placebo)
- Women had a mean age of 55 years (40-65) and a mean BMI of 27 kg/m^2 at study entry (**Table 1**); the mean number of hot flushes at baseline was 57

Table 1. Demographics and Baseline Characteristics of the Safety Population

Characteristic	Estradiol/Progesterone				Placebo
	1 mg/ 100mg	0.5 mg/ 100 mg	0.5 mg/ 50 mg	0.25 mg/ 50 mg	
n	415	424	421	424	151
Age, y	54.7 ± 4.4	54.5 ± 4.5	54.9 ± 4.3	54.4 ± 4.0	54.5 ± 4.3
Race, n (%)					
White	271 (65.3)	281 (66.3)	276 (65.6)	273 (64.4)	100 (66.2)
African American	134 (32.3)	136 (32.1)	133 (31.6)	140 (33.0)	46 (30.5)
Other*	10 (2.4)	7 (1.6)	12 (2.8)	11 (2.6)	5 (3.3)
BMI, kg/m^2	26.8 ± 4.1	26.7 ± 4.0	26.7 ± 4.0	26.7 ± 4.0	26.6 ± 3.9
Time since menopause, y	5.8 ± 4.9	6.0 ± 5.1	5.7 ± 4.6	5.6 ± 4.9	6.0 ± 5.3

Data presented as mean ± SD, unless stated otherwise.
SD, standard deviation; BMI, body mass index; VMS, vasomotor symptoms.
*Other includes: other (n=10), American Indian or Alaska Native (n=2), Native Hawaiian or Pacific Islander (n=2), and unknown (n=1).

Correlations between Hormone Levels and Study Outcomes

- Statistically significant inverse correlations (*P*<0.0001) between serum E2 and E1 concentrations at week 12 and frequency of hot flushes, severity of hot flushes, overall MENQOL score, MENQOL vasomotor domain score, and MOS-Sleep overall score at week 12 were found (**Table 2**)
- Endogenous (baseline) serum E2 and E1 concentrations were not correlated with hot flush, quality of life, or sleep outcome measures at baseline or at week 12 (except for E1 with hot flush frequency at week 12)
- Positive correlations were found between E2 and E1 levels at baseline and bleeding or spotting days/week at week 12 (*P*<0.01), and between hormone levels at week 12 with bleeding or spotting days/week at week 12 (*P*<0.001; **Table 2**)
- Serum concentrations of E2 and E1 at week 12 had a significant (*P*<0.0001) predictive value for ≥4 versus <4 vaginal bleeding or spotting days/week at week 12 (**Table 3**)

Disclosures

- Mr. Biehl was an employee of TherapeuticsMD at the time of the analysis and is currently enrolled at the Nova Southeastern University Kiran C. Patel College of Osteopathic Medicine, Davie, FL. Dr. Mirkin is an employee of TherapeuticsMD with stock/stock options. Dr. Bernick is an employee of TherapeuticsMD with stock/stock options and is also a Board member.
- TherapeuticsMD sponsored the REPLENISH trial and provided support for the medical writing assistance of Dominique Verlaan, PhD, CMPP (Precise Publications, LLC)

Table 2. Correlations Between Estradiol and Estrone Concentrations at Week 12 and Outcomes at Week 12

Outcome	Correlation Coefficient (r)		*P*-value
	Log [estradiol pg/mL]	Log [estrone pg/mL]	
Log [Frequency of hot flushes*]	-0.312	-0.309	<0.0001
Log [Severity of hot flushes*]	-0.254	-0.257	<0.0001
MENQOL total score	-0.176	-0.194	<0.0001
MENQOL vasomotor domain	-0.295	-0.323	<0.0001
MOS-Sleep overall score	-0.128	-0.150	<0.0001
MOS-Sleep Problems Index I	-0.124	-0.142	<0.0001
MOS-Sleep Problems Index II	-0.126	-0.148	<0.0001
Bleeding or spotting days/week	0.148	0.116	<0.0001

*Mild, moderate, or severe hot flushes.

Table 3. Odds Ratio for Predictive Values of Hormone Concentrations with Bleeding or Spotting Days/Week (≥4 Days vs <4 Days) at Week 12

Hormone	Odds ratio (95% CI)	*P*-value
Log [estradiol pg/mL]	9.34 (4.02-21.69)	<0.0001
Log [estrone pg/mL]	6.96 (2.69-18.02)	<0.0001

Conclusions

- Concentrations of E2 and E1 at week 12 inversely correlated with outcomes commonly measured in menopausal vasomotor symptom trials during week 12; higher levels of E2 or E1 were associated with improved outcome scores
  - Such correlations would be expected given the previously reported improvements in VMS,[2] the MENQOL questionnaire,[3] and the MOS Sleep Outcomes scale[4] with TX-001HR
- E2 and E1 concentrations also significantly predicted the likelihood of vaginal bleeding or spotting after 12 weeks of therapy
- The etiology of vasomotor symptoms warrants further investigation for developing a more comprehensive understanding of what factors can influence menopausal clinical outcomes

References

1. Mirkin S, et al. *Endocrine Reviews* 2018;39. **2.** Lobo RA, et al. *Obstet Gynecol* 2018;132:161-170. **3.** Simon J, et al. *Menopause* 2017;24:1432. **4.** Kagan R, et al. *Menopause* 2017;24:1431.

2018 Annual Meeting of the North American Menopause Society, October 3-6, San Diego, CA