Vaginal Physical Examination Correlates with Vaginal Epithelial Cells and pH and Can Be Used to Assess Treatment Efficacy

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Introduction
- Vulvar and vaginal atrophy (VVA), a common chronic condition of postmenopausal women, is assessed by objective (vaginal cells and vaginal pH) and subjective (symptom severity) measures.
- In clinical practice, healthcare providers (HCPs) often utilize vaginal visual assessments to diagnose VVA with patient-reported symptoms to determine appropriate treatment.
- Significant improvements in change from baseline to week 12 must be shown in vaginal superficial cells, parabasal cells, and pH and, improvement in the most bothersome moderate to severe symptom, for a drug to be approved in the U.S. for treating VVA.
- A recent study showed a correlation between visual examinations and objective measures with ospemifene.
- HCP visual assessments as a tool to diagnose VVA and assess response to local vaginal estrogens has not been established.

Objective
- To examine the relationship between HCP visual assessments on a physical exam of the vagina and objective measures (vaginal cells and vaginal pH) to determine if visual assessments are an appropriate way to establish patient need and responsiveness to VVA treatment.

Patients and Methods
- Healthy postmenopausal women (aged 40–75 years; BMI ≤34 kg/m²) were randomized to placebo gelcap (VagiCap™; TX-004 HR) or placebo gelcap for 14 days in this Phase 2 pilot, double-blind trial.
- Four physical visual assessments were evaluated: vaginal visual assessments; vaginal pH; vaginal atrophy; and vaginal color. Each assessment was graded on a 4-point scale, with a severity score of 0 corresponding to characteristics expected to be observed with no atrophy, 1 mild, 2 moderate, and 3 severe (Table 1).
- Visual assessments completed at baseline (day 1) and day 15 were evaluated to determine if visual assessments are an appropriate way to establish patient need and responsiveness to VVA treatment.

Statistical Analysis
- Vaginal visual assessments for the vaginal estradiol gelcap (TX-004 HR) and placebo groups were combined to determine whether visual assessments correlated with objective measures (Table 1).
- Correlations between this visual assessment sum and vaginal cell percentages and vaginal pH at baseline and change from baseline at day 15 were evaluated by Spearman rho.
- Differences in the shifts from one visual assessment category at baseline to a different category of severity at day 15 were compared between vaginal estradiol and placebo groups using Fisher’s exact test.
- A mixed model, repeated measurement analysis of variance was used to determine statistically significant differences in means for the 4 visual assessment grades within each cell type or vaginal pH at baseline and at day 15.
- A P-value < 0.05 was considered statistically significant.

Results

Subjectediposition and baseline characteristics
- Of the 50 women who were randomized (n=24 vaginal estradiol gelcap; n=26 placebo), 40 completed the study (7 women in the placebo group discontinued [consent withdrawal [n=1] and adverse events [n=1]; parabasal and vaginal atrophy]).
- Women (n=48) were a mean age of 62.5 ± 4.5 years and had a mean BMI of 26.9 ± 3.7 kg/m². Mean percentages of superficial, parabasal, and intermediate cells were 0.9 ± 2.0, 63.5 ± 39.1, and 38.5 ± 37.6, respectively.

Correlation of Vaginal Cell Types and pH and the Sum of Visual Assessments
- At baseline, significant correlations between parabasal and intermediate cell percentages and the sum of the 4 visual assessments were observed, independent of treatment (Table 2).
- Higher proportions of superficial cells were observed at baseline to observe a significant correlation.
- At day 15, parabasal cell percentages and vaginal pH significantly correlated with the sum of the visual assessments at all subjects were analyzed (Table 2; Figure 1).

Table 2. Correlation of Vaginal Cells and pH with the Sum of the Four Visual Assessments

<table>
<thead>
<tr>
<th>Vaginal Cell Type</th>
<th>Correlation Coefficient*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial (%)</td>
<td>0.12</td>
<td>0.4</td>
</tr>
<tr>
<td>Parabasal (%)</td>
<td>0.09</td>
<td>0.05</td>
</tr>
<tr>
<td>Intermediate (%)</td>
<td>-0.32</td>
<td>0.05</td>
</tr>
<tr>
<td>Vaginal pH</td>
<td>0.07</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Change from Baseline to Day 15
- Changes in vaginal visual assessment severity ratings were observed among women at the end of the study.
- Vaginal visual assessments were significantly different between vaginal estradiol gelcap versus placebo (Figure 2A–C).
- In general, more shifts from mild to moderate at baseline to no atrophy at day 15, or moderate at baseline to mild at day 15 (improvement) were seen with the vaginal estradiol gelcap than with placebo.

Vaginal Visual Assessments
- At baseline, no statistically significant comparisons were observed among severity grades within each cell type for vaginal visual assessments, vaginal estradiol gelcap versus placebo, or vaginal color. However, differences were observed at baseline between vaginal estradiol gelcap versus placebo for moderate vs. no atrophy.
- By day 15, significant differences in percentages of superficial cells were observed between mild versus no atrophy for vaginal estradiol gelcap (P=0.03) and intermediate cells (P=0.02) for moderate vs. no atrophy.
- Percentages of parabasal cells at day 15 were significantly different between mild versus no atrophy for vaginal estradiol gelcap (P=0.03) and placebo (P=0.06), and between moderate versus mild for vaginal epithelial thickness (P=0.02).

Vaginal pH
- At baseline, for all women, vaginal pH was significantly different for mild versus no atrophy for vaginal estradiol gelcap (P=0.04) and intermediate versus mild atrophy for vaginal estradiol gelcap (P=0.05).
- At day 15, vaginal pH was significantly different for mild versus no atrophy for vaginal estradiol gelcap (P=0.001) and moderate versus no atrophy for vaginal color, regardless of treatment (P=0.03).

Conclusions
- A new gap of 10 pg solubilized estradiol significantly improved vaginal epithelial integrity, vaginal secretions, and vaginal color relative to placebo. This is consistent with the first report of this pilot study showing significant improvements in vaginal maturation index, pH, and epithelial integrity and vaginal secretions.
- Vaginal visual assessments correlated with objective measures, including parabasal and intermediate cells at baseline and at day 15, and vaginal pH at day 15.
- This vaginal estradiol gelcap (4, 10, and 25 µg) is being studied in a phase 3 trial.

Visual assessments of the vagina by HCPs are shown here to be valid and reliable measures to diagnose VVA and assess response to treatment.

References

Disclosures
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