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Review

Emerging therapies for postmenopausal vaginal atrophy

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ABSTRACT

Symptoms related to vaginal atrophy are a significant problem for postmenopausal women and estrogen has been the gold standard for its treatment. A number of recent reviews of vaginal estrogen products are available. This review will, therefore, focus on other products and potential products for this indication, including the tissue selective estrogen complex and selective estrogen receptor modulators. Additionally, lesser-studied approaches will be discussed.

Contents

1. Introduction

In a recent Cochrane Collaboration review it was reported that in healthy women over age 60 about 50% have symptoms related to vaginal atrophy, which can include vaginal dryness, itching, irritation and dyspareunia [1]. In non-institutionalized Dutch women aged 50–75 the prevalence of vaginal dryness, soreness and dyspareunia was estimated to be 27% [2]. The North American Menopause Society estimated that 10–40% of postmenopausal women have symptoms of vaginal atrophy [3].

During the reproductive years, the vagina is in part protected by a pH in the range of 3.5–4.5. This results from the proliferative effect of estrogen on the vaginal epithelium, principally the intermediate and superficial cells, where glycogen is deposited. *Lactobacilli* metabolize the glycogen producing lactic acid and supporting the lower pH. With menopause and declining estrogen levels, the vaginal maturation index shifts toward parabasal cells

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and the pH increases. Vaginal pH measurements can be artificially elevated by blood, cervical mucus, semen, douches and vaginal medications, and hence should be avoided during measurements [4].

New drug applications for the treatment of vulvar–vaginal atrophy in the United States are evaluated by the Food and Drug Administration (FDA) and the related indication for estrogen products is for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. They recommend three co-primary efficacy endpoints in studies for this indication, evaluated based on the mean change from baseline to week 12 versus placebo. These endpoints include: (1) improvement in the most bothersome moderate to severe symptom identified by the patient; (2) lowering the vaginal pH; and (3) change in the vaginal maturation index (decrease in vaginal parabasal cells and increase in vaginal superficial cells). The symptoms identified by the patient include vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, and vaginal bleeding associated with sexual activity. The FDA recommends that postmenopausal women enrolled in studies for this indication have identified at least one most bothersome moderate to severe symptom, have a vaginal pH > 5 and have no greater than 5% superficial cells on their vaginal smear [5]. These recommendations may prove to be relevant to some drugs in addition to estrogens.

There are a number of reviews available on vaginal estrogen products for the treatment of vaginal atrophy as well as a Cochrane Collaboration review from 2003 and updated in 2006 and hence is not the focus of this paper [1,6–8]. This review will focus on recent publications related to other drugs for this indication.

2. TSECs

A tissue selective estrogen complex (TSEC) pairs a selective estrogen receptor modulator (SERM) with estrogen(s). The first TSEC to undergo regulatory review pairs bazedoxifene (BZA) with conjugated estrogens (CE). In a phase 3, 12-week study, two doses of BZA/CE, 20 mg/0.625 mg and 20 mg/0.45 mg were compared with BZA 20 mg and placebo. Participants were generally health postmenopausal women aged 40–65 with a body mass index of 34 kg/m^2 or less. At screening they were required to have 5% or fewer superficial cells on their vaginal cytological smear, a vaginal pH greater than 5, and to identify a moderate to severe vulvar/vaginal symptom most bothersome to them. The primary efficacy endpoints were those recommended in the FDA guidance. Six hundred and sixty-four women were randomized, 652 took at least one dose of study medication and 601 completed the study.

The increase in the percentage of superficial cells and the decrease in the percentage of parabasal cells from baseline to 12-weeks was significantly greater with both doses of BZA/CE compared with both placebo and BZA alone. The vaginal pH did not change significantly from baseline to 12-weeks in either the BZA alone group or placebo, but decreased significantly in both BZA/CE groups. However, the decrease in the mean vaginal pH was significantly lower than placebo only for the BZA/CE 20 mg/0.625 mg group. The most bothersome symptom improved significantly at 12-weeks compared to placebo in the BZA/CE 20 mg/0.625 mg group but not in the 20 mg/0.45 mg group. There were no significant differences among the groups in the percentage of women reporting treatment emergent adverse events (TEAEs) or in discontinuations due to adverse events. The BZA/CE groups also did not differ from placebo in gynecologic TEAEs, however, there was a significantly higher incidence of vaginitis in the BZA/CE groups compared with placebo [9].

3. SERMs

3.1. Lasofoxifene

Lasofoxifene 0.25 mg and 0.5 mg has demonstrated an effect in treating vulvovaginal atrophy in phase 3 studies. Over 12-weeks, compared to baseline, lasofoxifene significantly reduced the most bothersome moderate to severe vulvovaginal atrophy symptom, increased the percentage of vaginal superficial cells and decreased the percentage of parabasal cells. Lasofoxifene significantly decreased parabasal cells by approximately 40% and increased superficial cells by approximately 7% compared to placebo. Additionally, compared to placebo, it reduced the vaginal pH, approximately 0.8 for lasofoxifene and 0.2 for placebo. In the PEARL study after 5 years, lasofoxifene increased both the risk of VTE and pulmonary embolism. An elevated risk for endometrial cancer was not observed. Endometrial hyperplasia was found in 2, 3 and 0 women in the 0.5 mg, 0.25 mg and placebo groups respectively. An increase in all-cause mortality was also found with the 0.25 mg but not the 0.5 mg dose group [10,11].

3.2. Ospemifene

Ospemifene, 30 mg, and 60 mg, and placebo, were studied in a 12-week phase 3 trial of 826 postmenopausal women. Participants were 40–80 years of age, with 5% or less vaginal superficial cells, vaginal pH greater than 5.0, and at least one moderate to severe symptom of vulvovaginal atrophy. Body mass index was less than 37 kg/m^2 and participants had not used vaginal hormone therapy (HT) for at least 14 days or oral/transdermal HT for 60 days. Non-hormonal vaginal lubricant was also provided to all participants and its weekly use recorded in diaries.

At 4 and 12 weeks, ospemifene 30 mg and 60 mg showed statistically significant increase in vaginal superficial cells and statistically significant decreases in parabasal cells, relative to placebo. Additionally, vaginal pH was also significantly decreased at both time points relative to placebo. The most bothersome symptom of vaginal dryness was significantly decreased in both the 30 mg and 60 mg groups relative to placebo at 12-weeks, while dyspareunia was decreased only in the 60 mg group. During the study, the most frequently reported adverse event was hot flushes reported by 9.6%, 8.3%, and 3.4% of participants in the ospemifene 30 mg, 60 mg and placebo groups, respectively. Mean change in endometrial thickness from baseline to 12 weeks was 0.42 mm, 0.72 mm, and −0.02 mm in the ospemifene 30 mg, 60 mg and placebo groups, respectively [12].

4. Lesser-studied approaches

4.1. DHEA

In a 12-week study 216 postmenopausal women administered intravaginally at bedtime one ovule containing 0.25% (3.25 mg), 0.5% (6.5 mg), 1.0% (13 mg) DHEA or placebo. Of these, 114 women identified dyspareunia as their most bothersome symptom at screening and day 1. Additionally, they had ≤5% vaginal superficial cells and vaginal pH greater than 5.0. At 12 weeks this population of 114 women demonstrated in all three DHEA groups compared to placebo a statistically significant reduction in the percent of vaginal parabasal cells, increase in the percent of vaginal superficial cells, and decrease in vaginal pH. At 12 weeks compared to baseline the placebo group did not show a significant difference in parabasal cell or superficial cells but did show a decrease in pH. The severity score for dyspareunia decreased significantly from baseline to 12 weeks in the placebo group, however, the score significantly decreased