Drospirenone–Estradiol Offers Multiple Hormone Therapy Benefits

Speaker: David F. Archer, MD, Professor of Obstetrics and Gynecology, Eastern Virginia Medical School, and CONRAD Research Center, Norfolk, Virginia.

Estradiol (E₂) and drospirenone (DRSP) (Yasmin®, Berlex), a combination estrogen–progestin birth control tablet, has been shown to be safe and effective as hormone replacement therapy in postmenopausal women while offering benefits in terms of improvements in blood pressure, lipid profiles, and body weight.

Researchers enrolled 1,142 amenorrheic postmenopausal women in a multicenter, double-blind, randomized, parallel-group study of four continuous combinations of DRSP and E₂, compared with E₂ alone. The women were randomly assigned to receive the following for one year:

- E₂ 1 mg of monotherapy or DRSP 0.5 mg with E₂ 1 mg (the dosage approved by the Food and Drug Administration)
- DRSP 1 mg with E₂ 1 mg
- DRSP 2 mg with E₂ 1 mg
- DRSP 3 mg with E₂ 1 mg

Clinic visits were scheduled at two-, three-, or four-cycle intervals for 13 28-day cycles. Blood pressure and weight measurements were taken at these visits, and lipid profiles were determined in 210 women at the baseline evaluation and at cycles 7 and 13.

Women receiving DRSP/E₂ at all doses showed significant declines in total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and triglycerides and an increase in high-density lipoprotein-cholesterol (HDL-C), compared with those receiving E₂ monotherapy. Furthermore, for women taking the two lower doses of DRSP with E₂, apolipoprotein levels were significantly reduced when compared with E₂ therapy alone.

Women receiving E₂ alone reported weight gain, whereas women in three of four DRSP/E₂ groups reported weight loss. The fourth DRSP/E₂ group registered constant body weight.

Blood pressure did not change significantly in any of the five treatment groups.

Lasofoxifene Improves Symptoms of Vaginal Atrophy

Speaker: Gloria Bachmann, MD, Associate Dean of Women’s Health and Professor of Gynecology and Obstetrics/Medicine, Robert Wood Johnson Medical School, and Director, Women’s Health Institute, Robert Wood Johnson University Hospital, New Brunswick, New Jersey.

Lasofoxifene (Oporia™, Ligand/Pfizer), a next-generation selective estrogen receptor modulator (SERM), significantly improves signs and symptoms associated with vaginal atrophy in postmenopausal women.

Women receiving DRSP/E₂ or DRSP/E₃ at all doses showed significant declines in total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and triglycerides and an increase in high-density lipoprotein-cholesterol (HDL-C), compared with those receiving E₂ monotherapy.

In postmenopausal women, a next-generation selective estrogen receptor modulator (SERM) that improves symptoms of vaginal atrophy, a novel transdermal testosterone that increases the frequency of satisfactory sexual activity in premenopausal women, bisphosphonates to prevent and treat osteoporosis in premenopausal and postmenopausal women, and a transdermal system to relieve overactive bladder...
endpoints included the percentage of parabasal and superficial cells from the maturation index and vaginal pH. Safety evaluations and adverse drug events (ADEs) were also monitored.

Compared with the women taking placebo, the women in both active treatment groups improved in all four co-primary endpoints as early as the second week, with significance achieved by the eighth week. In the self-assessment of the most bothersome symptoms, at baseline, the most common one was dyspareunia (painful intercourse), reported in 40%, followed by vaginal dryness in 31%, dysuria in 16%, and vaginal or vulvar itching in 13% in all treatment groups.

All of the women studied had a mean baseline severity score of 2.4 for dyspareunia. By week 12, the adjusted mean decreases were 1.3 with lasofoxifene 0.25 mg/day, 1.4 with 0.5 mg/day, and 0.9 with placebo, a significant difference favoring active drug treatment in both groups versus placebo.

By week 12, the maturation index showed an adjusted mean decrease from baseline in the percentage of parabasal cells: 37.5% with lasofoxifene 0.25 mg/day, 36.8% with 0.5 mg/day, and 3.3% with placebo.

From baseline to week 12, the mean increase in the percentage of vaginal superficial cells was 5.9% with lasofoxifene 0.25 mg/day, 4.7% with 0.5 mg/day, and 2.5% with placebo.

The vaginal pH was significantly reduced with active treatment. By week 12, the adjusted mean decreases in vaginal pH from baseline values were 0.77 pH units with lasofoxifene 0.25 mg/day, 0.86 pH units with 0.5 mg/day, and 1.9 pH units with placebo.

Testosterone Enhances Sexual Activity in Premenopausal Women

Speaker: Susan Davis, MD, PD, Professor of Women’s Health, Monash University, Melbourne, Victoria, Australia.

In premenopausal women with low libido who have testosterone levels below the mid-normal range, daily administration of a newly developed testosterone metered-dose transdermal spray system (MDTS®, Acrux, Ltd.) may bring about an increased frequency of satisfactory sexual events.

A study was designed to evaluate the effect of a range of testosterone doses in premenopausal women, 35 to 45 years of age, who had experienced a decrease in satisfactory sexual activity from their younger years and who had low serum testosterone levels. This condition appears to be more common than previously thought.

Following a four-week assessment of the frequency of sexual activity at baseline, 261 women in a dose-ranging study were randomly assigned to one of four treatments: one of three active doses of testosterone (low, middle, or high) or placebo. A transdermal spray was applied topically to the abdomen once daily for 16 weeks, followed by a four-week post-treatment evaluation.

The primary efficacy variable was the number of satisfactory sexual events in each 28-day period after 16 weeks of treatment, as recorded and collected in a daily patient diary. Secondary variables included the frequency of these events at weeks 4, 8, 12, and 16; serum testosterone levels; and adverse drug effects.

At the beginning of the study, women in each of the four study groups reported a mean baseline frequency of 1.3 satisfactory sexual events. At the end of the study, there was a statistically significant increase in the primary endpoint in patients receiving the middle testosterone dose in the intent-to-treat population.

At week 16, the mean increase in satisfactory sexual events was 2.00 in the middle-dose patients and 0.53 in the placebo patients. Positive effects were actually seen at earlier time points, and a maximal significant effect was reached at 12 weeks.

Mean increases in serum testosterone levels were within the normal range for premenopausal women.

Alendronate May Prevent Bone Loss After Discontinuation of Estrogen Therapy

Speaker: Michael R. McClung, MD, Director, Oregon Osteoporosis Center, and Attending Physician, Endocrinology, Providence Portland Medical Center, Portland, Oregon.

Results from a comparison study indicate that alendronate (Fosamax®, Merck), a well-known bisphosphonate, may be more effective than raloxifene (Evista®, Lilly), a selective estrogen receptor modulator (SERM), in preventing bone loss and bone resorption in postmenopausal women after estrogen therapy.

Because estrogen deficiency after menopause results in a loss of bone mass and deterioration of the skeletal architecture, a study was designed to compare alendronate and raloxifene in postmenopausal women discontinuing estrogen to assess the tolerability and effects on bone density and bone turnover in a bisphosphonate versus a SERM.

A total of 124 postmenopausal women, all of whom had stopped taking estrogen within the previous six months, were randomly assigned to take alendronate 70 mg once weekly or raloxifene 60 mg once weekly, with a double placebo. All of the women received 1,000 mg of calcium and 400 International Units (IU) of vitamin D daily.

Bone mineral density (BMD) was measured in the lumbar spine, total hip, femoral neck, and hip trochanter at the baseline, at six months, and at 12 months. A marker for bone resorption in osteoporosis called urinary N-telopeptide was measured at the baseline, at three months, and at 12 months. The major endpoints included an evaluation of the mean percentage change in these areas at 12 months.

At 12 months, compared with baseline values, there were significant BMD increases in the lumbar spine (2.3%), total hip (1.1%), and proximal femur (1.3%). With raloxifene, by contrast, a marked decrease occurred in the lumbar spine (–1.4%), with a comparable loss in the proximal femur and little or no change in the total hip (–0.05%). Urinary telopeptide decreased significantly—by 48.3%—with alendronate but did not change with raloxifene.

All of these differences between patient groups were significant at all time points. BMD loss was greater for women receiving raloxifene than for those taking alendronate, and fewer women taking alendronate lost BMD.

The proportion of women who experienced a decrease in lumbar spine BMD of more than 3% at 12 months was only 1.8% with alendronate and 32.8% with raloxifene.
Intermittent IV Ibandronate May Be as Effective as Daily Oral Dosages for Osteoporosis

Speaker: E. Michael Lewiecki, MD, Director, New Mexico Clinical Research and Osteoporosis Center, Albuquerque, New Mexico.

Intermittent intravenous (IV) ibandronate (Boniva®, Roche/GlaxoSmithKline) is at least as effective and as well tolerated as daily oral ibandronate in postmenopausal women with osteoporosis, providing a viable treatment option for patients who are unable to receive or adhere to oral bisphosphonates.

The Dosing Intra-Venous Administration (DIVA) study was designed to identify the optimal IV ibandronate regimen and to assess its safety and efficacy. In this two-year, phase 3, randomized, non-inferiority clinical trial, 1,395 patients with postmenopausal osteoporosis were randomly assigned, in a 2:1:2:1 ratio, to one of four treatment arms:

- 2 mg of IV abandronate every two months plus daily oral placebo (two patients)
- 2.5 mg of oral ibandronate daily plus IV placebo injection every two months (one patient)
- 3.0 mg of IV abandronate every three months plus daily oral placebo (two patients)
- 2.5 mg of oral ibandronate daily plus IV placebo injection every three months (one patient)

All patients also received daily supplements of oral calcium 500 mg and vitamin D 400 IU.

The primary efficacy endpoint was the mean percentage range from baseline in lumbar spine (L2–L4) BMD after one year. Secondary efficacy endpoints included:

- mean percentage increases in proximal femur, lumbar spine, and total hip BMD at one year:
- mean serum creatinine percentage changes in both active treatment study arms.
- ADEs of special interest, including flu-like illness, renal ADEs, and clinical fractures.

At the one-year follow-up of patients in all treatment arms, the primary endpoint demonstrated substantial increases in lumbar spine L2–L4 BMD. Both IV regimens proved to be noninferior to the daily regimen. The BMD increases in the IV regimens, however, were greater than those shown in the daily oral arm: 5.1% with 2 mg IV every two months, 4.8% with 3 mg IV every three months, and 3.8% with the daily oral dosage.

For the secondary endpoints, gains in BMD were greater for patients taking 3 mg every three months than for those taking the daily oral dosage. Total hip and trochanter BMD gains were greater with 2 mg every two months, compared with the daily oral regimen.

Ultra-Low-Dose Transdermal Estrogen Appears Safe for Preventing Osteoporosis

Speaker: Deborah Grady, MD, MPH, Vice Chair and Professor of Epidemiology, Biostatistics, and Medicine, Department of Epidemiology, University of California, San Francisco (UCSF), and Director, UCSF Women’s Health Clinical Research Center, San Francisco, California.

Two years of treatment with an ultra-low-dose estradiol patch (Menostar™, Berlex) was effective in preventing osteoporosis without increasing mammographic breast density.

Increased mammographic breast density suggests an increased risk of breast cancer. Standard-dose oral estrogen therapy increases breast density in 10% to 40% of women, and adding progestin increases density in 30% to 50% of women.

A study was conducted to determine whether two years of treatment with a new estradiol patch, at 14 mcg/day, resulted in changes in the incidence of breast cancer during a two-year osteoporosis-prevention trial in postmenopausal women. All participants also received calcium 800 mg and vitamin D 400 IU daily.

This nine-center, two-year, randomized, blinded, placebo-controlled trial enrolled 417 postmenopausal women with normal bone density for their age, an intact uterus, and no history of breast cancer. Baseline and follow-up mammograms were obtained from 276 of the 319 participants enrolled at the three largest study clinical sites.

In the initial efficacy portion of the study, at month 24, increases in spinal and hip BMD, as well as decreases in biomarkers of bone turnover, were significantly more pronounced in the participants receiving ultra low-dose transdermal estradiol than in the women receiving placebo. The benefits were independent of the initial BMD or the presence of baseline osteoporosis risk factors.

There were no statistically significant differences between the treatment groups in absolute change or in the percentage of change in breast density at one or two years of treatment.

Risedronate Reduces Fracture Risk Regardless of Bone Mineral Density Changes during Treatment

Speaker: Paul D. Miller, MD, Program Chair and Clinical Professor of Medicine, University of Colorado Health Sciences Center, Denver, Colorado, and Medical Director, Colorado Center for Bone Research, Lakewood, Colorado.

An analysis of data from a number of large-scale clinical trials suggest that risedronate (Actonel®, Procter & Gamble), when compared with placebo, helps to reduce osteoporotic fractures in postmenopausal women, regardless of whether bone mineral density (BMD) is gained or lost.

Although risedronate 5 mg a day has previously demonstrated efficacy in preventing fractures independent of the patient’s baseline BMD status, it is debatable whether this efficacy is also independent of BMD changes experienced over the duration of therapy. A study was designed to determine the efficacy of risedronate in reducing the risk of fractures, whether vertebral or nonvertebral, in postmenopausal women who either gained or lost BMD during therapy.

This analysis included 2,846 women in the phase 3, three-year, placebo-controlled, fracture endpoint trials. A total of 1,428 patients received risedronate 5 mg daily, and 1,418 patients were given placebo. Lumbar spine and/or femoral neck BMD data were available at the baseline, at three years,
or at the last observation. Using a mathematical regression model and a hazard ratio, the investigators estimated the efficacy of risedronate 5 mg/day in reducing fracture risk.

The antifracture efficacy of the medication was statistically significant, compared with placebo, whether or not BMD was gained or lost at either the lumbar spine or the femoral neck. Furthermore, the magnitude of the drug’s efficacy was similar in the women whether there was a gain or loss of BMD either at the lumbar spine or femoral neck over the duration of treatment.

**Patients Appear Satisfied with Transdermal Oxybutynin Patches for Overactive Bladder**

**Speaker:** Lindsey A. Kerr, MD, Associate Professor of Urology and Director, Pelvic Floor Disorder Center, University of Utah Health Sciences Center, Salt Lake City, Utah.

Preliminary data indicate that a majority of patients report high levels of satisfaction with transdermal oxybutynin (Oxytrol Transdermal System®, Watson Pharma, Inc.) (TDS) and prefer the patch to other oral therapies for overactive bladder (OAB).

Although clinical trials of oxybutynin TDS for OAB have demonstrated the efficacy and safety of this approach, as well as a low incidence of anticholinergic effects that are commonly seen with oral medications for OAB, few data are available in terms of patient satisfaction with this transdermal treatment. The Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin (MATRIX) study was conducted to assess safety, health-related quality of life, and other patient-reported outcomes in a large patient population. This is an ongoing, open-label, randomized, multicenter prospective six-month study in community-dwelling adults with OAB.

To date, 2,878 patients (87% female) are receiving oxybutynin TDS 3.9 mg/day. Most of the participants (1,632 patients) have a history of having received OAB pharmacotherapy, and 32% have taken multiple ineffective medications.

For this initial analysis, 1,609 patients participated in telephone interviews, answering questions regarding their experience with the patch after one month of treatment. Overall, 69.6% of the women in the group were “very satisfied” or “satisfied” with oxybutynin TDS. Patients reported high levels of satisfaction with the product’s effectiveness, tolerability, and ease of application. Approximately 75% of patients considered oxybutynin TDS “very convenient” or “convenient,” and more than 65% of patients said that they were not bothered by (“aware of”) the patch during daily activities. Of patients who were “aware of” the patch, 71% said that it “rarely” or “never” affected their daily activities.

For patients who had received previous OAB therapy, 63.4% stated that oxybutynin TDS offered benefits over their previous treatments. As in the total study group, these patients were more satisfied with the ease of application, effectiveness, and tolerability compared with earlier therapies.