OBG MANAGEMENT

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New options in osteoporosis therapy: Combination and sequential treatment

Perhaps the biggest medical question to emerge from the WHI study is how to best treat postmenopausal osteoporotic women. Could the answer lie in combining 2 current monotherapies?

While the headline-grabbing Women's Health Initiative (WHI) study has been alerting clinicians and patients alike to the risks and benefits associated with hormone replacement therapy (HRT), a series of lower-profile investigations offers new hope to osteoporotic women.

KEY POINTS

- Combination or sequential therapy may benefit the approximately 15% of osteoporosis patients who continue to lose bone on monotherapy.
- Greater bone-density increases result from bisphosphonate plus either estrogen or raloxifene than from single-agent therapy.
- The introduction of parathyroid hormone (PTH) (1-34), a therapy that stimulates bone formation, will likely result in development of combination or sequential regimens of PTH plus an antiresorptive agent.
- Estrogen may be indicated early in the transition to menopause, but many authorities recommend switching to a bisphosphonate in late postmenopause.
- For menopausal women with a recent osteoporotic fracture, 1 month of calcitonin treatment may help increase bone density and reduce fracture pain. After the pain has resolved, a bisphosphonate, raloxifene, or PTH can be started.

Numerous clinical trials have demonstrated that approximately 15% of women with osteoporosis who are treated with a single drug continue to lose bone mass[1,2]; particularly resistant are cigarette smokers and women with a body weight below 130 lb.[3]

But recent studies suggest that combination therapy or sequential treatment may be effective for women:

- with severe osteoporosis,
- who continue to lose bone mass while taking a single pharmacologic agent, or
- who suffer a new fracture while on monotherapy.

No trials to date have shown that combination therapy definitively decreases the fracture rate compared to monotherapy; however, since BMD increases correlate closely with protection against fracture risk, it is likely that a study with adequate power will show a direct correlation.

Here, I review the most promising options.

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Combination therapy

The results of the WHI study indicate that estrogen has a complex pattern of risks and benefits in postmenopausal women.[4] Clinicians must therefore carefully assess the value of adding estrogen to another pharmacologic osteoporosis treatment for each individual woman.

Patients with menopausal symptoms—such as vasomotor symptoms or urogenital atrophy—are probably the best candidates for combination treatment with estrogen and another antiresorptive agent.

Estrogen plus alendronate. The combination of these 2 agents is probably more effective in increasing BMD than either agent alone.

▪ **Bone et al.**[5] For example, in 1 clinical trial, 425 postmenopausal women with osteoporosis were randomized to 1 of 4 treatment groups: conjugated equine estrogens (CEE) alone (0.625 mg daily), alendronate alone (10 mg daily), a combination of the two at the same doses, or placebo. All subjects received daily calcium supplementation (500 mg). After 2 years of treatment, women in the placebo group demonstrated a 0.6% loss in lumbar spine BMD, while patients treated with alendronate or CEE alone showed increases of 6%.

Those taking alendronate plus CEE, however, demonstrated a lumbar-spine BMD gain of 8.3%—an increase significantly greater than that of either monotherapy group ($P<.022$). In addition, women in the placebo group showed a 0.3% increase in BMD of the proximal femur, versus 4% for those taking alendronate, 3.4% for those given CEE, and 4.7% for those taking alendronate plus CEE. All active treatments were well tolerated by the participants.

The authors concluded that the combined use of alendronate and estrogen produced "somewhat larger increases in BMD than either agent alone."

▪ **Palumba et al.**[6] In another clinical trial, 150 surgically postmenopausal women with osteo-

Fundamentals of osteoporosis prevention and treatment

Diet

An optimal daily diet for preventing and treating osteoporosis includes:

- 1,000 mg to 1,500 mg of elemental calcium in divided doses with meals[1]
- Vitamin D 800 IU
- Sufficient calories to avoid malnutrition
- Adequate protein

In 1 clinical trial, protein supplementation of 20 g per day was associated with better bone-density preservation and faster rehabilitation after hip fracture than an isocaloric, nonprotein supplement.[2]

Drugs

The US Food and Drug Administration (FDA) has approved:

- Alendronate and risedronate (bisphosphonates) and raloxifene (selective estrogen receptor modulator) for prevention and treatment of osteoporosis (see **TABLE 1**).
- Calcitonin and parathyroid hormone (PTH) (1-34) for treatment only.
- Estrogen for preventing osteoporosis. (Although also effective for treating the disease, it is not specifically approved for this by the FDA.)

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TABLE 1

FDA-approved treatments*

DRUG	DOSAGE
Alendronate	70 mg once per week, orally
Risedronate	35 mg once per week, orally
Raloxifene	60 mg daily, orally
Calcitonin	200 IU daily, by intranasal insufflation
Parathyroid hormone	20 µg daily, by subcutaneous injection

*Cost of all agents is approximately $65 per month, except parathyroid hormone, which costs approximately $450 per month.

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Case 1: A family history of breast cancer

A 56-year-old woman presents with a recent bone density demonstrating T-scores of -3.2 at her hip and -2.4 at the lumbar spine. The patient had her last menstrual period at age 53. She experienced vasomotor symptoms for 8 months, but no longer has hot flashes.

Two years ago, her sister, then age 45, was diagnosed with bilateral breast cancer. There is no other family history of this disease. At the time of her sister's diagnosis, the patient had T-scores of -2.7 and -2.3 at the hip and lumbar spine, respectively. She was prescribed exercise, vitamin D 800 IU, and calcium supplements, as well as raloxifene 60 mg daily to both improve her bone density and reduce her risk of breast cancer.

A case for combination therapy. During the 2 years of raloxifene therapy, the patient's lumbar spine bone density stabilized but her hip bone density declined. At this follow-up visit, she underwent a series of tests for secondary causes of osteoporosis (**TABLE 2**). All results were within the normal range.

In this case, the addition of a second agent such as alendronate (70 mg once weekly) or risedronate (35 mg once weekly) is warranted to reverse the continued bone loss in her hip. It is likely that on combination therapy, her bone density will increase.[1] In addition, continued raloxifene treatment will reduce her risk of breast cancer—a major worry of hers due to her sister's illness.

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TABLE 2

Laboratory test results for secondary causes of osteoporosis and osteomalacia

CONDITION	LABORATORY TEST RESULT
Hyperparathyroidism	Elevated parathyroid hormone Elevated calcium Decreased phosphorus
Vitamin D deficiency	Decreased 25-hydroxyvitamin D
Hyperthyroidism	Decreased thyroid-stimulating hormone
Renal disease	Elevated phosphorus Decreased calcium

porosis were randomized to 2 years of therapy with 2 mg per day of micronized estradiol plus either placebo, standard-dose alendronate (10 mg daily), or low-dose alendronate (5 mg daily). Micronized estradiol plus alendronate at either the standard or low dose was associated with significantly greater increases in BMD than estradiol plus placebo.

▪ **Lindsay et al.**[7] A third clinical trial looked at 428 postmenopausal women with osteoporosis who were already being treated with estrogen for at least 1 year. Subjects were continued on estrogen and randomized to receive alendronate (10 mg daily) or a placebo. After 1 year of treatment, the women taking alendronate showed a significantly greater increase in lumbar-spine BMD (3.6% versus 1%, $P<.001$) and hip trochanter BMD (2.7% versus 0.5%, $P<.001$) than women taking placebo.

Alendronate plus raloxifene.

▪ **Johnell et al.**[8] In a clinical trial, 331 postmenopausal women with osteoporosis were randomized to receive placebo, raloxifene (60 mg daily), alendronate (10 mg daily), or raloxifene plus alendronate for 1 year.

While all active treatments produced significantly greater increases in BMD than did placebo, the combination group exhibited sig-

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Case 2: Halting hormone therapy in a young menopausal woman

A 48-year-old woman became menopausal at age 44. She was a 2-pack-per-day smoker for many years, but recently quit. At the early age of menopause onset, she began therapy with conjugated equine estrogen 0.625 mg daily and medroxyprogesterone acetate 2.5 mg daily. The patient had no hot flashes and no menses with this treatment.

Based on the media coverage of the Women's Health Initiative results, she recently decided to discontinue hormone replacement therapy. She knows this will result in an accelerated rate of bone loss and wonders what she should do. A bone density test demonstrates T-scores of -2.1 and -2.3 in the hip and spine, respectively. What would you advise?

A case for sequential therapy. In menopausal women, discontinuation of hormone replacement therapy is associated with a rapid loss of bone mineral density.[1] Now that this woman with osteopenia has discontinued her estrogen treatment, it is highly likely she will become osteoporotic unless a bone medicine is initiated.

Sequential therapy of hormone replacement followed by a bisphosphonate has been associated with an increase in bone density. For this woman, initiation of treatment with a bisphosphonate—alendronate 70 mg once weekly or risedronate 35 mg once weekly—is indicated to prevent a decline in bone density. In addition, regular exercise, vitamin D, and calcium supplements may help preserve her bone mass.

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nificantly greater increases than did either monotherapy group. The increases in lumbar-spine BMD in the raloxifene, alendronate, and raloxifene plus alendronate groups were 2.1%, 4.3%, and 5.3%, respectively; the increases in femoral-neck BMD were 1.7%, 2.7%, and 3.7%, respectively.

Parathyroid hormone (1-34). Intermittent administration of parathyroid hormone (PTH) (1-34) stimulates bone formation more than it stimulates bone resorption.

▪ **Neer et al.**[9] In 1 clinical trial, 1,637 postmenopausal women with a previous osteoporotic fracture were randomized to treatment with placebo or PTH monotherapy (20 μg or 40 μg daily by subcutaneous injection) for an average of 21 months. PTH treatment increased BMD compared with placebo. New vertebral fractures were documented in 14% of the women receiving placebo and 5% and 4% of women taking PTH 20 μg and 40 μg, respectively. New nonvertebral fractures were documented in 6% of those in the placebo group and 3% of those in each of the PTH groups. Side effects associated with PTH included nausea and headache.

The mechanism of PTH action is fundamentally different than that of antiresorptive agents such as alendronate, risedronate, raloxifene, and estrogen. Although combinations of PTH plus an antiresorptive agent have not yet been studied directly, it is likely that additive effects would be demonstrated.

▪ **Rittmaster et al.**[10] In 1 study of sequential treatment of postmenopausal women with PTH followed by alendronate, each for 1 year, investigators demonstrated that after 1 year of PTH therapy, alendronate treatment resulted in additional BMD increases much greater than those previously reported for alendronate or estrogen alone.[10]

Sequential treatment

Estrogen followed by a bisphosphonate. Because premenopause, perimenopause, and postmenopause are dynamic physiological

states, specific osteoporosis treatments may need to target different stages. For example, in premenopausal and perimenopausal women with osteoporosis, estrogen replacement therapy (ERT) may be indicated.[11-13] In early postmenopause, ERT may be warranted to treat both vasomotor symptoms and osteoporosis. Estrogen-progestin therapy is clearly effective in the treatment of osteoporosis. In the WHI study, the risk of osteoporotic fracture was reduced at both the hip (5 fewer hip fractures per 10,000 woman-years with a relative risk of 0.66; 95% CI, 0.45 to 0.98) and in the vertebral spine (relative risk 0.66; 95% CI, 0.44 to 0.98) for women receiving estrogen-progestin therapy compared to placebo.

The results of the WHI study have caused many women to discontinue estrogen therapy, but bone loss is significant in postmenopausal women in the first few years after discontinuing estrogen therapy.[14] Once the patient enters later stages of postmenopause, therefore, many authorities recommend switching from estrogen to a bisphosphonate, since bisphosphonates are not associated with a known risk of breast cancer or cardiovascular disease.

Calcitonin followed by a bisphosphonate. After an osteoporotic fracture, some women experience intense pain for 1 to 2 months. Calcitonin has been demonstrated to decrease pain associated with osteoporotic fractures significantly more than placebo.[15] One possible solution, therefore, is to use calcitonin (200 IU by nasal administration daily) for the first month after a painful osteoporotic fracture, followed by treatment with a bisphosphonate.

Looking ahead

In the next 12 months approximately 1.5 million new osteoporotic fractures will occur in American women. Given the data that indicate the life expectancy of a 65-year-old American woman is 20 years, it is likely that there will be a significant increase in the number of osteoporotic fractures in the next decade. According to community-based population studies, however, the majority of women with osteoporotic fractures do not receive adequate treatment for the disease.[16] Gynecologists play an important role in helping to increase the effectiveness of the prevention and treatment of osteoporosis. ■

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