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Effects of ospemifene on bone in postmenopausal women

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ABSTRACT

Ospemifene is a selective estrogen-receptor modulator approved for treating menopause-related moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy (VVA), in the United States, and for treating menopause-related, symptomatic VVA in women not appropriate for local estrogen therapy in Europe. This review summarizes the effects of ospemifene on bone, including bone biomarker data from a phase 3 vaginal dryness study. Early-phase studies of postmenopausal women showed that ospemifene dose-dependently decreased bone turnover markers versus placebo, similar to raloxifene. A 12-week, phase 3 study of ospemifene 60 mg/day in postmenopausal women showed improvements in all VVA parameters and significantly greater decreases in seven of nine bone biomarkers versus placebo. Lower bone resorption markers with ospemifene were observed regardless of time since menopause (≤ 5 years or > 5 years) or baseline bone mineral density (BMD) (normal [$n = 18$], osteopenia [$n = 164$], or osteoporosis [$n = 21$]). Biomarker studies ($n = 565$ who took ospemifene) therefore support a potential role for ospemifene in maintaining bone health (and possibly reducing fracture risk) in postmenopausal women taking it for VVA; however, caution is warranted because data are limited to biochemical markers, rather than fracture and BMD. Although studies show that bone turnover predicts BMD and fractures, any hypothesis about a bone-sparing effect of ospemifene needs testing in rigorous, long-term, phase 3 studies monitoring fractures and BMD.

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Introduction

Osteoporosis, a 'silent' progressive weakening in bone strength due to declining bone mass and bone quality, predisposes to fracture risk¹. Both osteoporosis and low bone mass (osteopenia) are associated with significantly elevated risk of fracture², and are highly prevalent in Europe and the United States with the incidence of both expected to rise over time^{3,4}. Osteoporotic fracture, which occurs in one in three women aged > 50 years worldwide⁵, is a serious consequence of osteoporosis; it negatively affects quality of life and is associated with increased mortality and health-care costs⁵⁻⁷.

Selective estrogen receptor modulators (SERMs) work through a mixed agonist/antagonist effect on estrogen receptors, mostly having varying agonist effects on bone⁸. Raloxifene is a SERM approved worldwide for treating and preventing osteoporosis in postmenopausal women and for reducing risk of invasive breast cancer in postmenopausal women with osteoporosis or at high risk of breast cancer⁹. Bazedoxifene is approved in Europe, Japan, and South Korea for the treatment of osteoporosis in postmenopausal women at high risk of fracture¹⁰.

Ospemifene is a SERM approved at 60 mg/day orally in the United States for the treatment of moderate to

menopause-related severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy (VVA), and in Europe for menopause-related, moderate to severe symptomatic VVA in women who are not candidates for local vaginal estrogen therapy^{11,12}. Because estrogen deficiency predisposes to both VVA and osteoporosis, there is great interest in studying the effects of ospemifene on bone health in postmenopausal women. The primary objective of this review was to summarize the effects of ospemifene on bone parameters and present new bone biomarker data from a recent phase 3 study¹³.

Methodology

PubMed was searched since its inception for articles pertaining to the effects of ospemifene on bone. Keywords in the search strategy included ospemifene and bone. Search results were reviewed for articles reporting primary clinical data on the effects of ospemifene on bone in postmenopausal women. Bibliographies of the included studies and reviews were also scanned for additional, relevant clinical studies.

Clinical trials

Phase 1 and 2 studies

Both phase 1 and phase 2 studies have evaluated the effects of ospemifene on bone, mostly by examining its effects on biochemical bone markers. Ospemifene doses of 25, 50, 100, and 200 mg/day were evaluated in 40 healthy postmenopausal women in a 12-week randomized, double-blind phase 1 clinical trial¹⁴. Ospemifene dose-dependently decreased procollagen type I N-terminal and C-terminal propeptides (PINP and PICP) and osteocalcin, but only the dose of 200 mg significantly ($p=0.01$) decreased bone-specific alkaline phosphatase (ALP) versus placebo¹⁴.

A double-blind, phase 2 study tested the safety and efficacy of ospemifene 30, 60, and 90 mg versus placebo in 159 healthy postmenopausal women ($n=30-40$ in each group) for 12 weeks¹⁵. Ospemifene induced a dose-dependent decrease from baseline relative to placebo in four of five bone markers tested (serum PINP, bone-specific ALP, and urinary C-terminal and N-terminal cross-linking telopeptides of type I collagen [CTX and NTX], but not PICP; all tests for linearity, $p \leq 0.03$)¹⁵. History of menopausal hormone therapy use was also associated with greater increases in NTX and CTX levels¹⁵. Thus, the effects on bone resorption suggested that ospemifene acted as an estrogen agonist, and that these effects were more prominent in women who had previously used menopausal hormone therapy¹⁵. Beneficial effects on bone markers declined 2–4 weeks after stopping ospemifene treatment¹⁵.

Ospemifene (30, 60, and 90 mg) was compared with raloxifene (60 mg) for bone resorption and bone formation markers in a 3-month, double-blind, phase 2 study of 118 healthy postmenopausal women ($n=29-30$ in each group)¹⁶. Bone resorption was assessed with urinary NTX and CTX, while bone formation was evaluated with serum PINP, PICP, bone-specific ALP, and osteocalcin¹⁶. Overall effects on bone markers were largely similar between the ospemifene and raloxifene groups¹⁶. Most treatment groups had a decline in bone markers, which were largest with ospemifene 60 mg and 90 mg, and raloxifene 60 mg¹⁶. There were no significant differences between ospemifene and raloxifene for CTX, PICP, ALP, or osteocalcin¹⁶.

Overall, phase 1 and 2 data on bone biomarkers suggest that ospemifene may have positive effects on bone, comparable to those exerted by raloxifene in postmenopausal women.

Phase 3 study

Study design and methodology

A 12-week multicenter, double-blind, randomized, placebo-controlled trial was conducted to evaluate the efficacy and safety of once-daily oral ospemifene 60 mg for the treatment of moderate to severe vaginal dryness as the most bothersome symptom of VVA due to menopause¹³. Eligible participants were healthy postmenopausal women aged 40–80 years who had moderate or severe vaginal dryness (rated as 0 = none; 1 = mild; 2 = moderate; and 3 = severe on

a validated questionnaire), $\leq 5\%$ superficial cells on vaginal wall smear, and vaginal pH > 5.0 at baseline¹³.

Women were randomized 1:1 to ospemifene 60 mg or matching placebo for treatment up to 12 weeks¹³. Randomization was stratified by moderate or severe vaginal dryness and the presence or absence of a uterus (limited to 60% of participants without a uterus in each group)¹³. The four co-primary efficacy endpoints were changes from baseline to week 12 in the percentages of vaginal parabasal cells and superficial cells, vaginal pH, and severity of self-reported vaginal dryness with ospemifene versus placebo¹³. Safety was assessed by treatment-emergent adverse events up to 14 days after the last dose¹³. Secondary endpoints included changes in five markers of bone resorption (bone sialoprotein, CTX, deoxypyridinoline, NTX, and tartrate-resistant acid phosphatase 5b [TRACP-5b]) and four markers of bone formation (serum total ALP, bone-specific ALP, serum osteocalcin, and PINP) from baseline to week 12.

Results

A total of 316 women were randomized to ospemifene and 315 women to placebo¹³. Demographics and baseline characteristics were similar between treatment groups¹³. The mean age was approximately 60 years, mean body mass index was 27.2 kg/m², and mean duration of VVA was 8–9 years¹³.

Serum levels of the nine bone biomarkers were similar between groups at baseline. When markers were measured as least-squares mean changes from baseline to week 12, the differences between treatment groups were negative for all bone resorption markers, with significantly greater decreases for ospemifene versus placebo for CTX, NTX, and TRACP-5b (all three comparisons, $p \leq 0.02$) (Table 1; Figure 1). Likewise, ospemifene was associated with greater least-squares mean decreases at week 12 for all bone formation markers compared with placebo (all comparisons, $p \leq 0.008$) (Table 2; Figure 2).

In a subgroup having baseline dual-energy X-ray absorptiometry, 118 women had normal bone parameters (≤ 5 years since menopause, $n=53$; >5 years since menopause, $n=65$), 164 had osteopenia ($n=60$ and $n=104$, respectively), and 21 had osteoporosis ($n=7$ and $n=14$). Definitions of osteoporosis (2.5 standard deviations below the young adult mean) and osteopenia (>1 but <2.5 standard deviations below the young adult mean) were used according to the World Health Organization criteria¹⁷. Biomarker data varied by baseline dual-energy X-ray absorptiometry/bone mineral density (BMD) and by years since menopause. Women in early menopause (≤ 5 years) and later menopause (>5 years) had numerically lower values for bone resorption markers with ospemifene versus placebo, and the benefit appeared to apply regardless of baseline BMD (normal, osteopenia, or osteoporosis), although the osteoporosis group was too small to allow definitive conclusions. It is further assumed that women in early menopause, who have an accelerated rate of bone resorption, may trend toward a larger treatment effect with ospemifene than would women in later menopause. Most biochemical bone markers numerically support

Table 1. Changes at week 12 in markers of bone resorption with ospemifene versus placebo^a.

Marker	Ospemifene 60 mg (n = 313)	Placebo (n = 314)	Difference of LS, mean (95% CI)	p-Value
BSP (pg/ml)				
Baseline				
n	304	312		
Mean (SD)	39,014.6 (201,567.4)	31,722.8 (158,379.3)		
Change, BL to week 12				
n	264	271		
LS mean (SE)	-24,964.3 (3922.5)	-20,576.1 (3871.5)	-4388.3 (-15,214.8, 6438.3)	0.4263
CTX (ng/ml)				
Baseline				
n	301	303		
Mean (SD)	0.428 (0.221)	0.438 (0.219)		
Change, BL to week 12				
n	261	260		
LS mean (SE)	-0.044 (0.008)	0.006 (0.008)	-0.049 (-0.071, -0.027)	<0.0001
DPD (μmol/mol)				
Baseline				
n	304	310		
Mean (SD)	6.75 (2.34)	6.96 (2.47)		
Change, BL to week 12				
n	261	260		
LS mean (SE)	0.08 (0.16)	0.22 (0.16)	-0.14 (-0.58, 0.29)	0.5159
NTX (nmolBCE/l)				
Baseline				
n	304	311		
Mean (SD)	14.46 (4.81)	14.50 (5.27)		
Change, BL to week 12				
n	265	270		
LS mean (SE)	-0.10 (0.23)	0.65 (0.23)	-0.75 (-1.39, -0.10)	0.0227
TRACP-5b (U/l)				
Baseline				
n	304	312		
Mean (SD)	3.41 (1.36)	3.54 (1.46)		
Change, BL to week 12				
n	265	270		
LS mean (SE)	-0.28 (0.04)	-0.06 (0.04)	-0.22 (-0.34, -0.10)	0.0003

BL, baseline; BSP, bone sialoprotein; CI, confidence interval; CTX, C-terminal cross-linking telopeptides of type I collagen; DPD, deoxypyridinoline; LS, least-squares; NTX, N-terminal cross-linking telopeptides of type I collagen; SD, standard deviation; SE, standard error; TRACP-5b, tartrate-resistant acid phosphatase 5b; BCE, bone collagen equivalent.

^aTo calculate LS means, SE, 95% CI, and p-value, an analysis of covariance (ANCOVA) model was used. The ANCOVA model has terms for the treatment group as a fixed effect and the baseline value as a covariate.

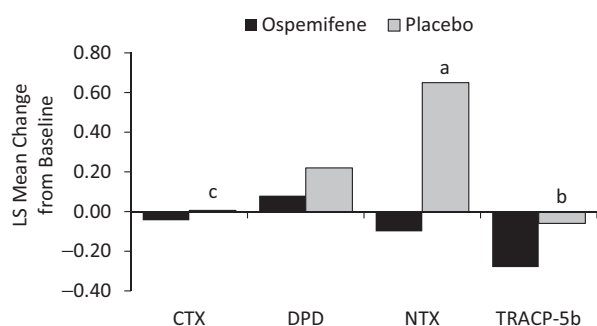


Figure 1. LS mean changes from baseline for bone resorption markers with ospemifene versus placebo at week 12. ^a $p < 0.05$; ^b $p < 0.001$; ^c $p < 0.0001$. CTX, C-terminal cross-linking telopeptides of type I collagen; DPD, deoxypyridinoline; LS, least-squares; NTX, N-terminal cross-linking telopeptides of type I collagen; TRACP-5b, tartrate-resistant acid phosphatase 5b.

the hypothesis that women taking ospemifene had an attenuation of bone loss when compared with women assigned to placebo.

Discussion

Clinical studies support a potential role for ospemifene in maintaining bone health in postmenopausal women while

they are taking it for the treatment of moderate to severe VVA. Serum levels of bone biomarkers in 565 women who received ospemifene in phase 1, phase 2, and phase 3 studies had significantly greater mean decreases from baseline to week 12 relative to placebo for most of the bone resorption and bone formation markers studied.

Clinical studies and animal models indicate that ospemifene has effects on bone markers significantly better than those of placebo and similar to those exerted by oral estrogens and other SERMs (i.e. raloxifene and bazedoxifene) approved for osteoporosis treatment and prevention. As described earlier, clinical studies in postmenopausal women showed that ospemifene administration induced a dose-dependent decrease of bone turnover markers relative to placebo¹⁵, with an effect similar to that of raloxifene¹⁶.

In animal studies, the effects of ospemifene on bone were similar to those with raloxifene or estradiol, or in sham-operated (versus ovariectomized [OVX]) animals^{18,19}. An OVX rat model showed that both ospemifene and raloxifene exert bone protective effects, decreasing bone turnover and maintaining bone volume¹⁸, although varying effects on osteoclast expression¹⁹ suggest that ospemifene and raloxifene have different mechanisms of action, which warrants further evaluation. Animal data further support positive effects of

Table 2. Changes at week 12 in markers of bone formation with ospemifene versus placebo^a.

Marker	Ospemifene 60 mg (n = 313)	Placebo (n = 314)	Difference of LS, mean (95% CI)	p-Value
ALP (U/l)				
Baseline				
n	312	314		
Mean (SD)	81.9 (21.0)	83.2 (23.9)		
Change, BL to week 12				
n	258	261		
LS mean (SE)	-4.6 (0.7)	1.6 (0.7)	-6.2 (-8.1, -4.3)	<0.0001
Bone-specific ALP (U/l)				
Baseline				
n	304	311		
Mean (SD)	24.92 (8.27)	24.57 (8.24)		
Change, BL to week 12				
n	265	270		
LS mean (SE)	-0.50 (0.36)	0.84 (0.36)	-1.35 (-2.35, -0.35)	0.0084
Osteocalcin (ng/ml)				
Baseline				
n	304	312		
Mean (SD)	23.60 (10.54)	23.58 (9.45)		
Change, BL to week 12				
n	265	270		
LS mean (SE)	-1.43 (0.31)	0.62 (0.31)	-2.06 (-2.92, -1.19)	<0.0001
PINP (ng/ml)				
Baseline				
n	301	303		
Mean (SD)	49.36 (20.60)	50.09 (21.10)		
Change, BL to week 12				
n	261	260		
LS mean (SE)	-3.22 (0.85)	2.04 (0.86)	-5.26 (-7.64, -2.89)	<0.0001

ALP, serum total alkaline phosphatase; BL, baseline; CI, confidence interval; LS, least-squares; PINP, procollagen type I N-terminal propeptide; SD, standard deviation; SE, standard error.

^aTo calculate LS means, SE, 95% CI, and p-value, an analysis of covariance (ANCOVA) model was used. The ANCOVA model has terms for the treatment group as a fixed effect and the baseline value as a covariate.

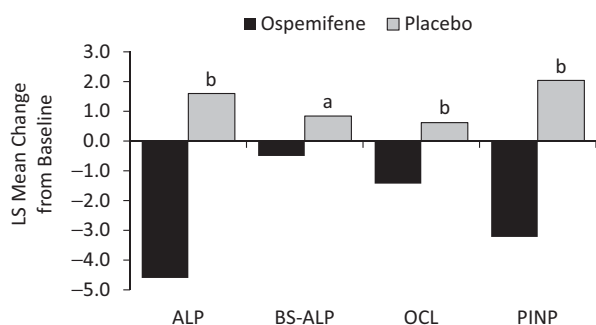


Figure 2. LS mean changes from baseline for bone formation markers with ospemifene versus placebo at week 12. ^a $p < 0.01$; ^b $p < 0.0001$. ALP, serum total alkaline phosphatase; BS-ALP, bone specific serum total alkaline phosphatase; LS, least-squares; OCL, osteocalcin; PINP, procollagen type I N-terminal propeptide.

ospemifene on bone mineral content, BMD, bone histology, and bone strength^{18,19}. When given to OVX rats at 1, 5, or 25 mg/kg for 1 year, ospemifene prevented decreases in bone mineral content and BMD in the femur and tibia in a dose-dependent manner relative to an untreated OVX group (all $p \leq 0.01$)¹⁹. Ospemifene 10 mg/kg for 4 weeks significantly prevented loss of trabecular bone volume and preserved bone strength in the femur and lumbar vertebrae in OVX rats (all $p < 0.05$ versus OVX controls), with effects comparable to those of 40 or 50 $\mu\text{g}/\text{kg}$ estradiol^{18,19}.

These findings with ospemifene suggest similar effects on bone as reported in phase 3 randomized trials showing significant decreases in osteocalcin and CTX with bazedoxifene (10, 20, or 40 mg) and raloxifene (60 mg) versus placebo at all time points from 3 to 24 months (all doses versus placebo,

$p < 0.001$)²⁰. Decreases in these bone markers were sustained with 60 mg raloxifene versus placebo after 24 months ($p < 0.05$)²¹ and 36 months ($p < 0.001$)²² of treatment in postmenopausal women at risk for osteoporosis.

Clinical implications

Phase 3 trials suggest that ospemifene may be beneficial to the bone health of women who are taking it to treat VVA. Animal and clinical studies demonstrate that ospemifene is superior to placebo in reducing bone turnover. In addition, improvements in CTX and osteocalcin similar to those reported with raloxifene and bazedoxifene suggest that ospemifene may be hypothesized to improve BMD (and possibly reduce fracture risk) in postmenopausal women while they are taking it to treat VVA.

Caution is warranted, however, because current clinical data for the effects of ospemifene on bone are limited to changes in biochemical markers. On the other hand, several studies have demonstrated a correlation between biochemical markers of bone turnover and both BMD and fractures. A literature review from the International Osteoporosis Foundation concluded that increased levels of bone resorption markers (above the upper limit of the premenopausal range) elevate the risk of fractures by approximately two-fold, and that bone markers may be used to assess fracture risk if BMD data are not available²³. The Malmö Osteoporosis Prospective Risk Assessment (OPRA) study found that elevations of urine osteocalcin, serum CTX, and serum TRACP-5b were associated with any type of fracture in women (all

$p < 0.05$ for clinical vertebral fractures)²⁴. Urine osteocalcin and serum TRACP-5b were also associated with hip fractures, at least one fracture, and multiple fractures (all $p < 0.05$) in these women. The Os des Femmes de Lyon (OFELY) study of healthy, untreated postmenopausal women reported a two-fold increase in relative risk for osteoporotic fractures in women with the highest baseline urinary CTX and serum CTX levels (relative risk 2.3 and 2.1, respectively; both $p = 0.01$), and this risk was maintained even after adjusting for body weight, height, and prevalent fractures²⁵.

Data from the Multiple Outcomes of Raloxifene Evaluation (MORE) study also suggest a correlation between bone biomarkers and fracture risk²⁶. A subgroup analysis of 2722 women treated with raloxifene for 12 months found a greater decrease in vertebral fracture risk in those women who had significant reductions in serum osteocalcin ($p = 0.003$) and bone ALP ($p = 0.005$) from baseline²⁶. In another MORE report of raloxifene treatment for 3 years, the percent decrease in osteocalcin from baseline to 1 year was a better predictor of reduced vertebral fracture risk at 3 years than was the percent increase in femoral neck BMD at 1 year, regardless of whether women had a prevalent fracture at baseline; in fact, the 2-year percentage decrease in osteocalcin could account for 34% of the decrease in vertebral fracture risk²⁷.

If ospemifene has effects on bone biomarkers similar to those of estrogens and other approved SERMs in postmenopausal women, and given that changes in bone markers may predict protection from fracture, then these same beneficial effects of preventing bone loss and fracture risk may be seen in women taking ospemifene for relief of VVA. However, such a hypothesis would need to be tested and proven in rigorous, long-term phase 3 clinical studies monitoring fractures and BMD, similar to several studies that documented significant increases in BMD and decreases in fractures with raloxifene and bazedoxifene treatment versus placebo in postmenopausal women with osteoporosis^{22,28,29}. Preliminary subgroup analyses also suggest that ospemifene decreases values of bone resorption markers with numerically better effects than placebo, particularly in early menopause (≤ 5 years), a time of accelerated bone loss.

Conclusions

Bone biomarker data in conjunction with animal bone quality data suggest that ospemifene does have bone-protective properties, and, thus, may provide a potential additive bone benefit for women who take ospemifene to treat VVA. These data support further studies to evaluate bone protection with ospemifene in postmenopausal women.

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