Osteoporos Int (1999) 9:358–366

Osteoporosis International

Original Article

Matrix Delivery Transdermal 17β-Estradiol for the Prevention of Bone Loss in Postmenopausal Women

C. Cooper[1], J. A. Stakkestad[2], S. Radowicki[3], P. Hardy[4], C. Pilate[4], M. P. Dain[4], P. D. Delmas[5] for The International Study Group*

[1]Southampton General Hospital, Southampton, UK; [2]Cecor AS, Haugesund, Norway; [3]Medical Academy of Warsaw, Warsaw, Poland; [4]Rhône-Poulenc Rorer, Antony, France; [5]Hôpital Edouard Herriot, Lyon, France

Abstract. A total of 277 early postmenopausal women were enrolled in this placebo-controlled 2-year study to examine the efficacy of a matrix transdermal 17β-estradiol system, at three different dosages (25, 50 and 75 μg/day) combined with sequential oral dydrogesterone 20 mg/day, in preventing bone loss. At 2 years, the difference from placebo in percentage change from baseline of L1–4 lumbar spine bone mineral density (BMD) (assessed by dual-energy X-ray absorptiometry) was 4.7% ± 0.7% with estradiol 25 μg/day, 7.3% ± 0.7% with estradiol 50 μg/day and 8.7% ± 0.7% with estradiol 75 μg/day (all values mean ± SEM). There were also significant increases in femoral neck, trochanter and total hip BMD with all doses of estradiol compared with placebo. Additionally, most patients had a significant gain (increase greater than 2.08%) in lumbar spine bone mass compared with placebo. Patients who received estradiol also experienced clinically significant and dose-related decreases in total serum osteocalcin, serum bone alkaline phosphatase and urinary C-telopeptide, with all three markers of bone turnover returning to premenopausal levels. Estradiol was well tolerated during the 2-year treatment period. Transdermal estradiol is effective and well tolerated at dosages between 25–75 μg/day in the prevention of bone loss in postmenopausal women; 25 μg/day offers an effective option for those women who cannot tolerate higher doses.

Keywords: Bone turnover; Menopause; Transdermal estradiol

Correspondence and offprint requests to: Professor Cyrus Cooper, Professor of Rheumatology, MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK. Tel: +44 (1703) 777 624. Fax: +44 (1703) 704 021. e-mail gjs@mrc.soton.ac.uk.

*International Study Group: Dr M. F. J. Bemelmans, Dr A. J. M. Boermans, Dr R. H. J. Brouwers, Dr P. Chevalier, Prof. C. Cooper, Prof. P. D. Delmas, Dr M. Dierick-Steen, Dr E. F. Eriksen, Dr P. Garnero, Dr M. Gunnes, Dr H. Joosten, Dr R. Kolthof, Dr G. M. D. Crawford, Dr S. de Meij, Dr P. Passage, Dr S. Pors-Nielsen, Prof. S. Radowicki, Dr F. de Ruiter, Dr A. C. J. Schlösser, Dr J. A. Stakkestad, Dr W. Schubert, Dr I. Smith, Dr D. J. M. van der Voort.

Introduction

Postmenopausal osteoporosis is a serious age-related disorder that affects millions of women throughout the world, and is a major cause of morbidity and mortality [1,2]. Estimates suggest that approximately 40% of women will experience one or more fractures after the age of 50 years [3].

At the menopause, bone turnover increases, with a greater increase in bone resorption than in bone formation [4]. Most bone is lost during the first 3–6 years after the menopause, followed by a smaller but steady decline [5].

Nowadays estrogen deficiency is considered to be the main factor leading to bone loss in postmenopausal women. It is well documented that hormone replacement therapy (HRT) initiated soon after the menopause reduces or even reverses the bone loss that normally occurs at this time [6,7] and reduces the incidence of osteoporotic fractures in postmenopausal women [7,8]. Cumulative data in the literature show that long-term estrogen use is associated with a 50% reduction in the rate of fractures [9].

Estrogen decreases bone remodeling, thus preserving bone mass and the microarchitectural quality of bone tissue. Therefore to prevent the acute bone loss that occurs immediately after the menopause, it is important that HRT should begin as early as possible and be maintained throughout the period of accelerated bone loss.

Various estrogens are available for clinical use, but the natural hormone, 17β-estradiol, which is the predominant estrogen produced by the ovaries in premenopausal women, is the logical choice for HRT. However, when given orally 60–90% of the dose of 17β-estradiol is metabolized to estrone in the gut mucosa, and estrogens are inactivated by glucuronidation in the liver. Thus, high oral doses (0.625 mg/day of conjugated equine estrogens or 2 mg/day of micronized estradiol) are required to achieve serum concentrations of 17β-estradiol adequate for the prevention of bone loss. For this reason, non-oral formulations of 17β-estradiol, which avoid first-pass metabolism, have been developed; these include vaginal, subcutaneous, percutaneous and transdermal systems.

Transdermal administration of 17β-estradiol has been widely used over the last decade and has been shown to be clinically effective, with the added benefits of being non-invasive, easy to use, and well-accepted by patients [10,11]. Transdermal 17β-estradiol systems have been shown to have bone-sparing effects at a dosage of 50 μg/day [12–14].

Menorest is a transdermal system in which 17β-estradiol is uniformly dispersed in an adhesive matrix. It has been shown to be effective in treating vasomotor symptoms [15,16] and to be better tolerated than reservoir patches [15]. The objective of this placebo-controlled study was to examine the efficacy of 2 years' treatment with a range of estradiol dosages in preventing bone loss in early postmenopausal women.

Subjects and Methods

Experimental Subjects

A total of 277 ambulatory women, aged 40–60 years, with a natural or surgical (bilateral oophorectomy) menopause for 1—6 years, serum follicle stimulating hormone (FSH) >34.4 mIU/ml and serum estradiol <30 pg/ml were eligible for inclusion. Other inclusion criteria were: a L1–4 spine bone mineral density (BMD) within 3.0 standard deviations (SD) below the mean of healthy young women (i.e. between 1.047 and 0.717 g/cm^2 with dual-energy X-ray absorptiometry (DXA) Hologic or between 1.180 and 0.820 g/cm^2 Lunar), a normal, clinically acceptable Papanicolaou (PAP) smear, and a normal mammogram within the previous year.

Exclusion criteria were: any condition contraindicating the use of HRT; severe postmenopausal symptoms (either mean number of hot flushes >10/day in the 2 weeks before the baseline visit, or symptoms considered as severe and disabling that required HRT); lumbar scoliosis impairing DXA examination; a history of non-traumatic vertebral or femoral fracture; a body mass index (BMI) >30 kg/m^2; any disease affecting bone metabolism; or any untreated endocrine or metabolic disease.

Any previous treatment for osteoporosis, or treatment within the previous 6 months with calcitonin, estrogens or vitamin D >800 IU/day was not permitted. Patients were also excluded if they required chronic use of treatments that interfere with bone metabolism (except the study medication) or chronic use (>8 days) of drugs that interfere with estrogen metabolism.

Study approval was obtained from appropriate ethics committees before the inclusion of patients, and written informed consent was obtained from each patient before participation.

Study Design

This randomized, double-masked, dose-ranging, placebo-controlled study was carried out in 19 centers in Denmark, The Netherlands, Norway, Poland, Sweden and the United Kingdom between December 1993 and November 1996. Patients were randomly allocated to one of the four therapeutic groups: transdermal 17β-estradiol patches (Menorest, Rhône-Poulenc Rorer) delivering 25 μg/day ($n=69$), 50 μg/day ($n=69$) or 75 μg/day ($n=70$), or placebo ($n=69$), applied twice weekly. Non-hysterectomized patients also received oral dydrogesterone 10 mg or placebo (placebo patients) twice daily for the last 14 days of each 28-day cycle. Treatment continued for 2 years. All patients had an assured total dietary calcium intake of 1 g/day, including a calcium supplement of 500 mg/day if necessary. Patients were assessed at the initial assessment 2–4 weeks before the baseline visit, and after 3, 6, 9, 12, 15, 18, 21 and 24 months of treatment, and in the case of premature discontinuation of therapy.

Outcome Measures

The primary efficacy criterion was the percentage change versus baseline in lumbar spine BMD after 2 years' treatment. Secondary efficacy criteria included: gain in lumbar spine bone mass after 2 years' treatment; percentage changes from baseline in femoral neck, trochanter, total hip and total body BMD; and the percentage change in biochemical markers of bone metabolism.

Methodology

During the study, DXA BMD assessments were performed for each patient using the same densitometer and, preferably, the same operator. Two centers used Lunar, while the other centers used Hologic densitometers. A quality control procedure was established to ensure correct and uniform analysis throughout all study

centers with specific instructions for all aspects of instrument operation. A coordinating center trained at least one operator from each study center and conducted site certification and follow-up visits to assess the skill of operators and equipment performance. The coordinating center also reviewed all scans for correct patient positioning, scanning and analysis technique and, if necessary, re-analyzed scans. It also provided phantoms to establish the equivalence of all the equipment. All correction factors, determined by the longitudinal QC using internal phantoms, were $<1\%$. The in vivo short-term precision error of the measurement was 1.04%.

Lumbar spine (L1–4) and hip (femoral neck, trochanteric region, Ward's triangle, intertrochanteric region (Hologic only) and whole area) BMD were performed at the initial assessment and after 6, 12, 18 and 24 months of treatment, and if treatment was prematurely discontinued (unless the last BMD had been performed within the previous 3 months). Total body BMD was also assessed, if the DXA machine was equipped with the appropriate software, at the initial assessment and after 12 and 24 months of therapy, and if treatment was prematurely discontinued (unless the last BMD had been performed within the previous 6 months). Patients whose BMD increased by more than twice the short-term coefficient of variation (i.e., $>2.08\%$) were considered to have gained bone mass; patients whose BMD decreased by this amount were considered to have lost bone mass.

Centralized laboratory assessments were made at the initial assessment and after 3, 6, 12, 18 and 24 months of therapy, and in the case of premature discontinuation (if the interval between last patch removal and termination day was $\leqslant 15$ days). Serum estradiol was quantitated by radioimmunoassay (RIA; Estradiol 125I Sensitive ORION Diagnostica). Blood was analyzed centrally by RIA for total osteocalcin (ELSA-OSTEO, CIS Bio Int, France) and bone-specific alkaline phosphatase (Ostase, Hybritech Inc, USA); urine was analyzed for type 1 collagen C-telopeptide (CTX; Crosslaps; Osteometer A/S, Denmark, France) corrected for creatinine. The intra-assay variability for the estradiol, osteocalcin, alkaline phosphatase and urinary C-telopeptide assays was $<20\%$, $<6\%$, $<12\%$ and $<8\%$, respectively.

Adverse events were evaluated from investigators' questioning and by patients volunteering information. Patients recorded skin adverse events on diary cards.

Compliance was monitored by the investigator using patient diary cards and from unused medication returned to the investigator. If compliance fell below 75% over the 2-year study period, the patient was excluded from the evaluable population.

Statistical Analyses

Two patient populations were used to analyze efficacy: the intention-to-treat (ITT) population and the per protocol population. The ITT population, which was used to analyze measurements of bone mass, consisted of all patients who were randomized to treatment and who had a baseline and at least one post-treatment measurement of lumbar spine BMD. For those patients who withdrew prematurely from the study, for whatever reason, the last measurement of lumbar spine BMD was carried forward as the study endpoint. The per protocol population, which was used to analyze markers of bone turnover, consisted of all evaluable patients who had measurements of the relevant parameters at the end of the study.

All statistical tests were two-sided at the 5% significance level. Treatment group differences in efficacy parameters were analyzed using a two-way analysis of variance with treatment groups and center as fixed blocking factors, and each active treatment group was compared with placebo using a pairwise step-down procedure maintaining a familywise error rate of 5% [17].

Results

Description of Treated Population

All 277 enrolled patients received study medication; 69 were randomized to placebo and 208 to active treatment with 17β-estradiol (25 μg/day, ($n=69$); 50 μg/day, ($n=69$); 75 μg/day, ($n=70$). A total of 212 patients completed the 2-year study: 74% of patients in the placebo group, and 78%, 80% and 74% in the 25, 50 and 75 μg/day groups, respectively. The 65 patients who withdrew prematurely from the study did so primarily because of adverse events (17%, 13%, 13% and 19% in the placebo, 25, 50 and 75 μg/day groups, respectively).

The main patient characteristics at baseline are shown in Table 1. In general, there were no major differences between the groups, and there were no clinically relevant differences in L1–4 lumbar spine, femoral neck, trochanter, total hip or total body BMD, as measured by Hologic or Lunar densitometers.

Efficacy Assessments

A total of 35 patients enrolled in the study were excluded from the ITT analysis ($n=242$) because of absent baseline or post-baseline L1–4 spine BMD measurements, while 76 were excluded from the per protocol analysis ($n=201$) for biochemical markers of bone metabolism because of protocol deviations.

After 2 years' treatment there were clinically relevant and statistically significant ($p=0.0001$) increases in L1–4 spine BMD in all the active treatment groups, compared with a decrease in the placebo group (Table 2). At 2 years the difference from placebo in percentage change from baseline of L1–4 lumbar spine BMD was 4.7% ± 0.7% with 17β-estradiol 25 μg/day, 7.3% ± 0.7% with 50 μg/day and 8.7% ± 0.7% with 75 μg/day (all values mean ± SEM). Figure 1 shows that the increase in

Table 1. Patients' baseline demographic data and clinical characteristics

		17β-Estradiol		
	Placebo (n = 69) (%)	25 μg/day (n = 69) (%)	50 μg/day (n = 69) (%)	75 μg/day (n = 70) (%)
Caucasian	68 (98.6)	69 (100)	68 (98.6)	69 (98.6)
Age (years)				
mean ± SD	53.3 ± 3.1	53.6 ± 3.1	53.2 ± 3.9	53.1 ± 3.5
BMI (kg/m^2)				
mean ± SD	24.3 ± 3.0	25.2 ± 2.8	25.6 ± 2.6	25.0 ± 2.9
Time since menopause (months)				
mean ± SD	38.7 ± 18.8	39.1 ± 18.0	42.3 ± 19.2	41.8 ± 18.7
Previous estrogen				
Yes	3 (4.3)	4 (5.8)	6 (8.7)	3 (4.3)
No	66 (95.7)	65 (94.2)	63 (91.3)	67 (95.7)
Type of menopause				
Natural	46 (66.7)	45 (65.2)	58 (84.1)	45 (64.3)
Natural + hysterectomy	22 (31.9)	24 (34.8)	11 (15.9)	22 (31.4)
Oophorectomy	1 (1.4)	0	0	3 (4.3)
Estradiol (pg/ml)				
mean ± SD	12 ± 11	12 ± 10	12 ± 11	12 ± 10
FSH (mIU/ml)				
mean ± SD	70 ± 23	71 ± 22	72 ± 25	77 ± 25
Calcium supplementation				
No	24 (34.8)	31 (44.9)	32 (46.4)	30 (42.9)
Yes	45 (65.2)	38 (55.1)	37 (53.6)	40 (57.1)
ITT population	n = 61	n = 58	n = 60	n = 63
L1–4 spine BMD T-score mean ± SD	–1.43 ± 0.9	–1.69 ± 0.8	–1.46 ± 0.9	–1.40 ± 0.78
Per protocol population	n = 49	n = 51	n = 52	n = 49
Serum total osteocalcin (ng/ml)				
mean ± SD	26.4 ± 10.6	24.4 ± 9.8	27.1 ± 7.7	27.8 ± 9.8
Bone-specific alkaline phosphatase (ng/ml)				
mean ± SD	13.7 ± 4.7	13.2 ± 4.7	14.1 ± 5.0	14.9 ± 4.8
Urinary CTX/creatinine (μg/mmol)				
mean ± SD	342.7 ± 159.6	330.2 ± 173.6	288.7 ± 123.4	339.9 ± 179.9

SD, standard deviation; BMI, body mass index; FSH, follicle stimulating hormone; ITT, intention-to-treat; CTX, C-telopeptide.

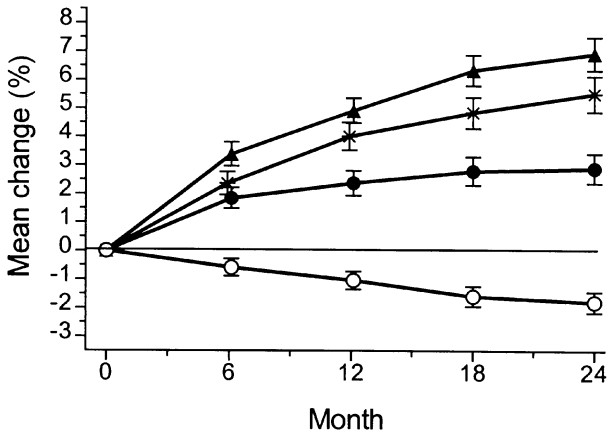

Fig. 1. Mean percentage change (± SEM) from baseline in lumbar spine bone mineral density (BMD) by visit and by treatment group in the intention-to-treat (ITT) population. Subjects received placebo (*open circles*) or 17β-estradiol 25 μg (*filled circles*), 50 μg (*crosses*) or 75 μg (*triangles*) daily.

L1–4 spine BMD was dose-dependent with 17β-estradiol, with larger increases during the first year of treatment.

At the end of the study, the majority of patients (63.8–88.9%) who received active treatment had a significant ($p = 0.0001$) gain in lumbar spine bone mass, compared with only 8.2% in the placebo group (Table 2).

There were significant increases from baseline in femoral neck ($p \leqslant 0.0025$), trochanter ($p = 0.0001$) and total hip ($p \leqslant 0.0004$) BMD in all the active treatment groups compared with the placebo group (Table 2). Figure 2 shows the percentage change in femoral neck, trochanter and total hip BMD throughout the 2-year study.

Over the 2-year study there was a continuous decrease in total body BMD in the placebo group compared with no change in the 25 μg/day group and small increases in the 50 and 75 μg/day groups (Table 2, Fig. 3). The difference between each active treatment group and the placebo group was significant ($p = 0.0001$).

Table 2. Mean change (± SEM) in efficacy parameters from baseline after 2 years' therapy in the intention-to-treat population. A gain in lumbar spine BMD was defined as an increase from baseline of ⩾2.08% (i.e., at least twice the short-term coefficient of variation)

		17β-Estradiol		
	Placebo (n = 61)	25 μg/day (n = 58)	50 μg/day (n = 60)	75 μg/day (n = 63)
L1–4 spine BMD (%)	–1.79 ± 0.37	2.90 ± 0.52	5.53 ± 0.63	6.94 ± 0.58
p value vs placebo	–	0.0001	0.0001	0.0001
Proportion of patients with lumbar spine BMD gain (%)	8.2	63.8	76.7	88.9
p value vs placebo	–	0.0001	0.0001	0.0001
Femoral neck BMD (%)	–2.04 ± 0.49	0.49 ± 0.57	3.07 ± 0.64	3.21 ± 0.67
p value vs placebo	–	0.0025	0.0001	0.0001
Trochanter BMD (%)	–1.45 ± 0.50	2.58 ± 0.64	3.51 ± 0.54	5.07 ± 0.55
p value vs placebo	–	0.0001	0.0001	0.0001
Total hip BMD[a] (%)	–1.03 ± 0.35	1.23 ± 0.45	3.12 ± 0.46	4.29 ± 0.49
p value vs placebo	–	0.0004	0.0001	0.0001
Total body BMD[b] (%)	–2.26 ± 0.30	0.23 ± 0.28	0.73 ± 0.36	1.58 ± 0.44
p value vs placebo	–	0.0001	0.0001	0.0001

BMD, bone mineral density.
[a]n = 47, 46, 47 and 49 for placebo, 25, 50 and 75 μg/day, respectively.
[b]n = 36, 36, 39 and 38 for placebo, 25, 50 and 75 μg/day, respectively.

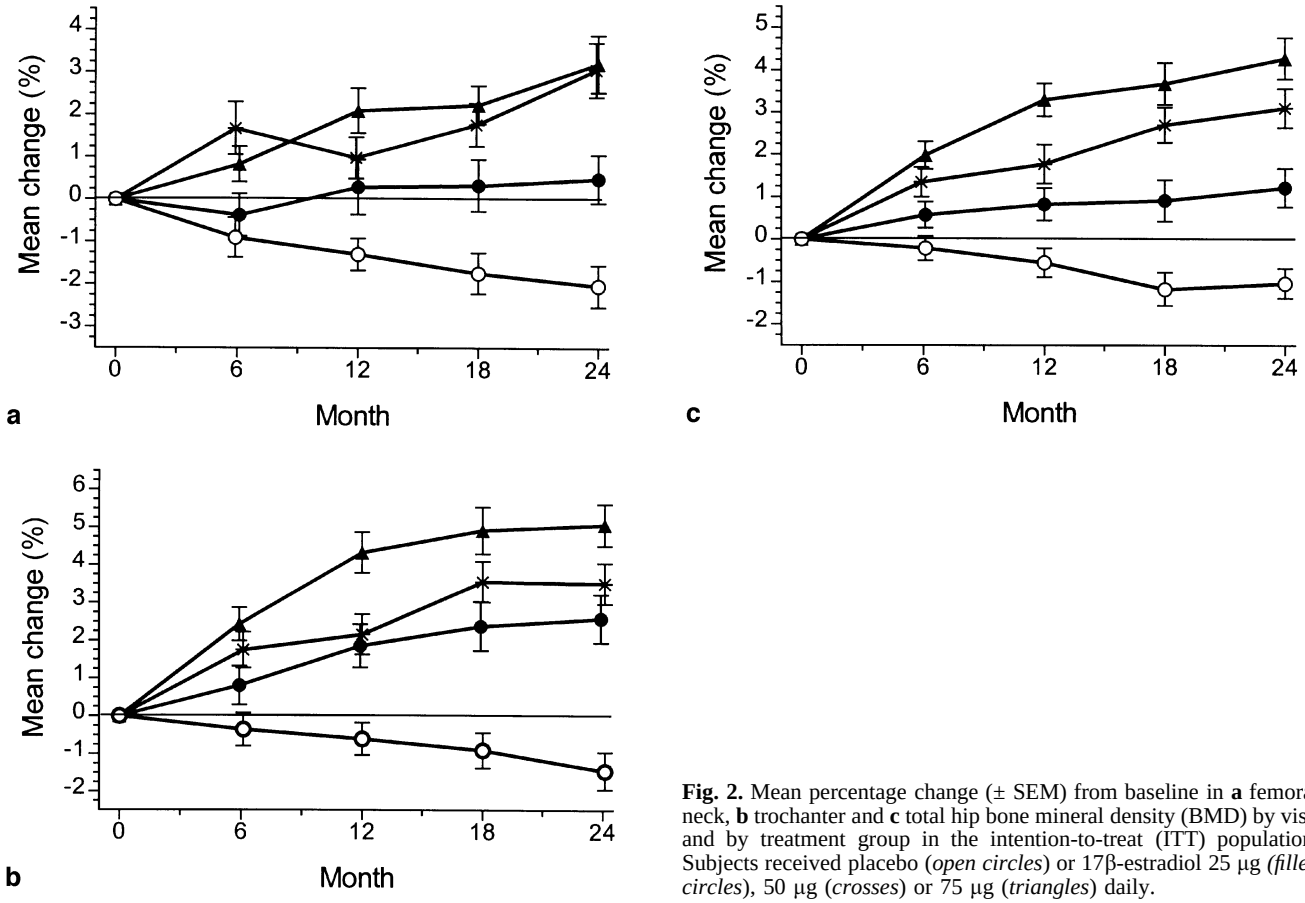

Fig. 2. Mean percentage change (± SEM) from baseline in **a** femoral neck, **b** trochanter and **c** total hip bone mineral density (BMD) by visit and by treatment group in the intention-to-treat (ITT) population. Subjects received placebo (*open circles*) or 17β-estradiol 25 μg *(filled circles*), 50 μg (*crosses*) or 75 μg (*triangles*) daily.

The number of patients with significant bone loss at each skeletal site was markedly decreased with active therapy relative to placebo at all tested doses (Table 3). With the exception of one value for femoral neck, the decreases were dose-dependent at all measured sites. There was no apparent difference in bone loss when patients were categorized according to time since menopause, possibly due to the low numbers of actively treated patients who lost bone (data not shown).

In the per protocol population there were clinically significant and dose-related decreases in total serum osteocalcin ($p \leqslant 0.0005$), serum bone alkaline phospha-

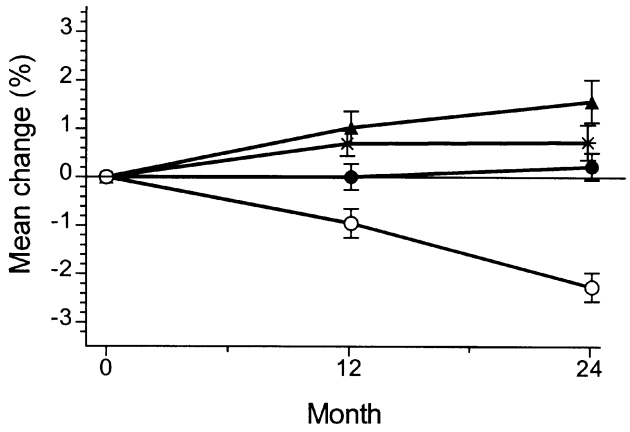

Fig. 3. Mean percentage change (± SEM) from baseline in total body bone mineral density (BMD) by visit and by treatment group in the intention-to-treat (ITT) population. Subjects received placebo (*open circles*) or 17β-estradiol 25 μg (*filled circles*), 50 μg (*crosses*) or 75 μg (*triangles*) daily.

tase ($p = 0.0001$) and urinary C-telopeptide ($p = 0.0001$) after 2 years' treatment with 17β-estradiol compared with placebo (Table 4). Figure 4a shows that there was a continuous decrease in total serum osteocalcin over the whole study (50 and 75 μg/day groups). Serum bone-specific alkaline phosphatase decreased in all the active treatment groups during the first 18 months, and there was a marked decrease in urinary C-telopeptide during the first 3 months of active treatment with levels then remaining stable for the rest of the study (Fig. 4b,c). In contrast, corresponding values in the placebo group remained essentially unchanged over the 2-year period.

When change in lumbar spine BMD at 2 years was analyzed by categorical time since menopause (1–3 years and 3–6 years), there was a significant treatment-by-subgroup effect indicating a dose effect dependent on the duration of menopause, with greater gain in women with the longer duration of menopause ($p = 0.011$; Fig. 5). The increases in the 3–6 year subgroup were 2.0 times and 1.8 times those in the 1–3 year subgroup for the 50 and 75 μg/day groups, respectively. Analysis of lumbar spine BMD according to baseline lumbar spine *T*-score ($T \geqslant -1$ SD, $n = 73$; -1 SD $> T \geqslant -2.5$, $n = 129$; or $T < -2.5$ SD, $n = 40$), did not show a significant treatment-by-subgroup effect ($p = 0.84$; data not shown).

Tolerability

All 277 patients enrolled were included in the analysis of safety. There were no deaths during the study and no significant differences between the groups in the number of patients who experienced at least one adverse event. Overall, the most frequent adverse events were:

Table 3. Number (%) of patients with BMD loss after 2 years' therapy in the intention-to-treat population. A loss in BMD was defined as a decrease from baseline of $\geqslant 2.08\%$ (i.e., at least twice the short term coefficient of variation)

		17β-Estradiol		
	Placebo (n = 61)	25 μg/day (n = 58)	50 μg/day (n = 60)	75 μg/day (n = 63)
L1–4 spine	25 (41.0%)	10 (17.2%)	3 (5.0%)	1 (1.6%)
Femoral neck	28 (45.9%)	18 (31.0%)	4 (6.7%)	7 (11.1%)
Trochanter	26 (42.6%)	10 (17.2%)	5 (8.3%)	3 (4.8%)
Total hip[a]	17 (36.2%)	9 (19.6%)	2 (4.3%)	2 (4.1%)
Total body[b]	22 (61.1%)	3 (8.3%)	5 (12.8%)	3 (7.9%)

BMD, bone mineral density.
[a]n = 47, 46, 47 and 49 for placebo, 25, 50 and 75 μg/day, respectively.
[b]n = 36, 36, 39 and 38 for placebo, 25, 50 and 75 μg/day, respectively.

Table 4. Mean percentage change (s.e.m.) in biochemical markers of bone turnover from baseline after 2 years' therapy in the per protocol population

		17β-Estradiol		
	Placebo (n = 49)	25 μg/day (n = 51)	50 μg/day (n = 52)	75 μg/day (n = 49)
Serum total osteocalcin (%)	3.92 ± 3.67	–9.01 ± 6.90[a]	–34.90 ± 2.98	–44.19 ± 2.77
p value vs placebo	–	[a]	0.0001	0.0001
Bone-specific alkaline phosphatase (%)	–2.86 ± 2.99	–24.51 ± 3.29	–30.73 ± 3.32	–38.71 ± 2.36
p value vs placebo	–	0.0001	0.0001	0.0001
Urinary CTX/creatinine (%)	11.35 ± 7.13	–39.49 ± 4.96	–43.46 ± 6.27	–63.46 ± 3.66
p value vs placebo	–	0.0001	0.0001	0.0001

[a]–14.55 ± 4.21; $p = 0.0005$ ($n = 50$) when one patient outlier is excluded (this patient had an abnormally low baseline value).

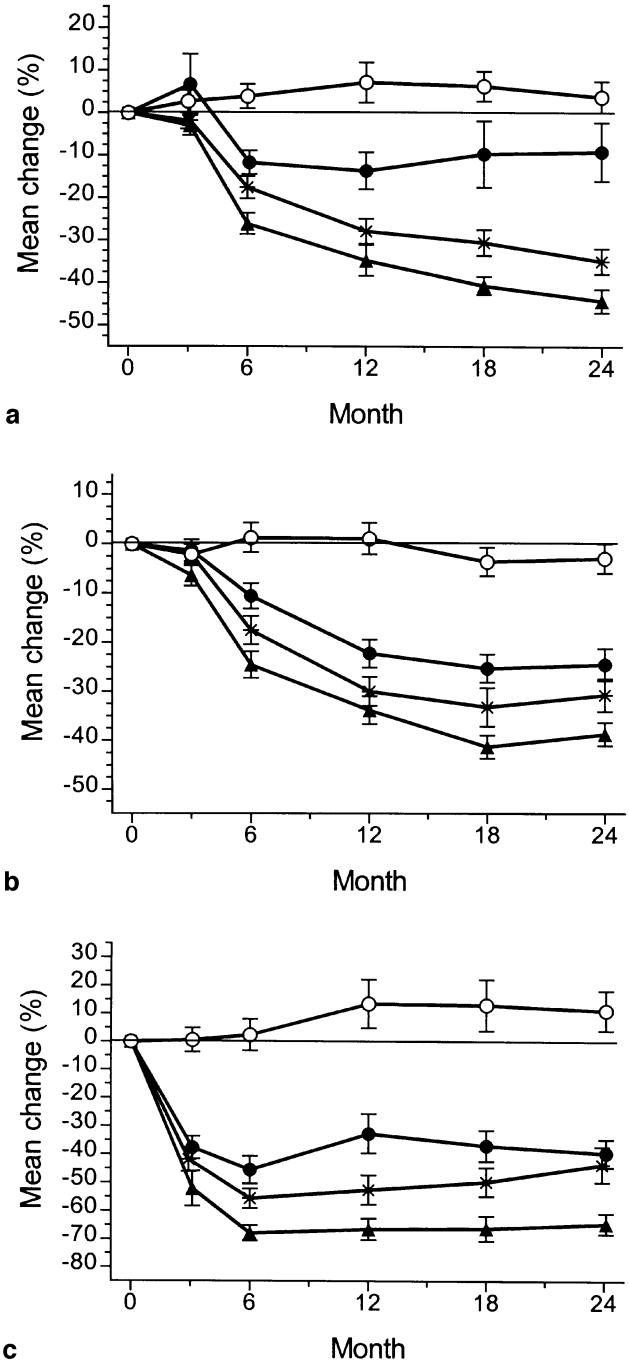

Fig. 4. Mean percentage change (± SEM) from baseline in **a** serum total osteocalcin, **b** serum bone-specific alkaline phosphatase and **c** urinary C-telopeptide (CTX) by visit and by treatment group in the per protocol population. Subjects received placebo (*open circles*) or 17β-estradiol 25 μg (*filled circles)*, 50 μg (*crosses*) or 75 μg (*triangles*) daily.

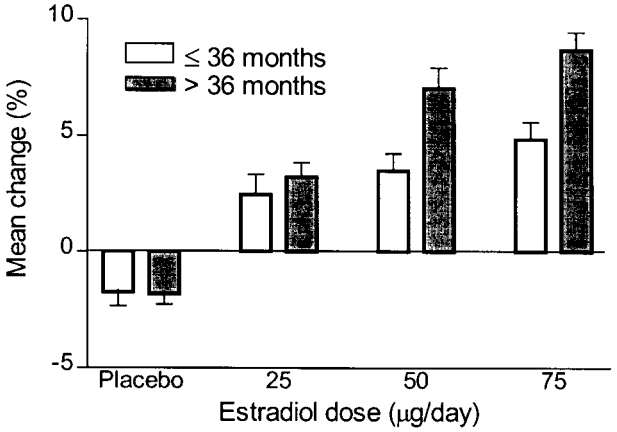

Fig. 5. Mean percentage change (± SEM) from baseline in lumbar spine BMD after 2 years' therapy, in patients with up to 36 months' menopause (n = 131) or more than 36 months (n = 111), in the intention-to-treat population.

application site reactions, headache, rhinitis, abdominal pain, 'flu syndrome, back and breast pain. Most adverse events were classified as mild-to-moderate and, except for application site reactions and breast pain, were not generally considered to be related to the study medication.

At the baseline visit, the majority of patients (⩾93%) reported having no breast tenderness during the previous 3 months. After 3 months of treatment, 9 (14.5%) placebo patients reported breast tenderness, compared with 26 (39.4%), 33 (54.1%) and 42 (63.6%) in the 25, 50 and 75 μg/day groups, respectively. Thereafter, the number of patients with breast tenderness decreased and at the end of the study it was reported by 4 (8.2%), 10 (18.9%), 5 (9.3%) and 11 (21.2%) patients in the placebo, 25, 50 and 75 μg/day groups, respectively.

A total of 14 patients had serious adverse events (5 in the placebo group and 4, 1 and 4 in the 25, 50 and 75 μg/day 17β-estradiol groups, respectively). However, this was only thought to be possibly related to the study medication (75 μg/day 17β-estradiol) in one patient who experienced jaundice and somnolence.

Pharmacokinetics

A linear relationship was found between serum estradiol concentrations, including the placebo group, and dose. Steady-state median values were very stable between visits: median ranges 5.0–7.0, 20.0–22.0, 35.5–43.0 and 52.0–57.5 pg/ml for the placebo, 25, 50 and 75 μg/day groups, respectively. Changes in lumbar spine BMD over time could be related to estradiol levels using a polynomial regression model:

$$\% \text{ BMD change} = 2.8263 + 0.2936\ E_2 - 0.0018\ (E_2)^2$$

where E_2 is the concentration of estradiol in picograms per milliliter (R^2 = 0.43; n = 198).

Discussion

This randomized, double-masked, dose-ranging, multicenter, placebo-controlled study of 277 postmenopausal women aged 40–60 years examined the efficacy of 2 years' treatment with three different doses of a novel

transdermal estradiol delivery system given continuously with a sequential progestin. Baseline demographic characteristics were comparable across all the treatment groups.

After 2 years' treatment there were significant increases in lumbar spine BMD in all active treatment groups compared with baseline values and the placebo group. Furthermore, significantly more patients in the active treatment groups gained lumbar spine bone mass at the end of the study compared with the placebo group. Active treatment also resulted in significant increases in femoral neck, trochanter and total hip BMD versus baseline compared with decreases in the placebo group. Total body BMD was measured only at those centers with densitometers equipped with the appropriate analytical software. However, despite the smaller number of patients in this analysis, the difference between each active treatment group and the placebo group at the end of the study was also significant and dose-dependent. Thus, all the beneficial effects on BMD of treatment with 17β-estradiol were dose-dependent. In particular, to our knowledge this is the first major study to demonstrate sustained and significantly superior efficacy over placebo of a daily 25 μg dose, supplemented by up to 500 mg calcium where necessary, in the prevention of bone loss. Others, for example, have compared the effects of 3 years' treatment with 25 and 50 μg/day of 17β-estradiol using a different transdermal delivery system and found no dose-dependent effects [18].

It has previously been demonstrated that the beneficial effects of estrogen on bone are only maintained during active therapy, and that discontinuation of treatment results in an immediate resumption of bone loss at a rate comparable to that seen in untreated controls [19]. Since there is an accelerated phase of acute bone loss during the first 3–6 years after menopause [5], it is crucial to maintain active therapy throughout this period. To minimize side-effects during long-term HRT treatment and therefore reduce the likelihood of treatment discontinuation, it is important to use the lowest therapeutically effective dose of estrogen. Until now it has been widely accepted that 50 μg/day of transdermal 17β-estradiol was the minimum dosage required to prevent lumbar spine loss in postmenopausal women [14]. However, the study demonstrating this effect was conducted in bilaterally ovariectomized women, who may well require higher doses than women with natural menopause, as in the present study. Our results suggest that 17β-estradiol at doses as low as 25 μg/day induces significant increases in bone mass, and also confirm the benefit of current 37.5 μg delivery systems.

Previous studies have demonstrated that the Menorest delivery system allows transdermal release of estradiol at a constant and reproducible rate at doses ranging from 25 to 100 μg/day [20]. There is also a linear relationship between the dose of estradiol administered (determined by the patch area) and its serum concentration [20]. In a 1-year, randomized dose-response study of patients treated with estradiol implants, changes in bone density were clearly shown to correlate with estradiol plasma levels [21]. The present study confirmed these results, and demonstrated that serum estradiol concentrations were maintained at or above the classical target of 40 pg/ml with doses $\geqslant$50 μg/day. As expected, serum estradiol concentrations in the 50 and 75 μg/day groups correlated with greater increases in lumbar spine BMD. However, this study clearly demonstrates that a dose of 25 μg/day, which delivered a median concentration of around 20 pg/ml, was nevertheless significantly effective relative to placebo.

Interestingly, there was a statistically significant relationship between the time since menopause and the change in lumbar spine BMD. Patients with a menopause more than 3 years before the start of therapy had larger increases in BMD, suggesting that the capacity of estrogen-sensitive tissues to respond to estrogen therapy increases with the period of estrogen deprivation. In order to maximize bone preservation, however, therapy may begin immediately after the menopause with 50 μg/day 17β-estradiol. This dosage may then be decreased to 25 μg/day 3–4 years after the menopause, i.e., after the period of accelerated bone loss, which may help compliance.

The major effect of estrogen therapy in postmenopausal women is to reduce bone turnover, with bone resorption decreasing more than bone formation [22]. During this 2-year study there were clinically significant and dose-related decreases in the biochemical markers of bone turnover with 17β-estradiol compared with placebo. Decreases in the levels of the bone resorption marker, urinary C-telopeptide, were greater than those of the bone formation markers serum total osteocalcin and serum bone-specific alkaline phosphatase. In the active treatment groups urinary C-telopeptide, serum total osteocalcin and serum bone-specific alkaline phosphatase levels had returned to premenopausal values after 3, 12 and 18 months of treatment, respectively. These results are consistent with a delayed fall in the rate of bone formation in response to the decrease in the rate of bone resorption, and are consistent with the observed increases in BMD.

The combination of 17β-estradiol and dydrogesterone was generally well tolerated, with similar incidences of adverse events in the active and placebo groups. Most adverse events were of mild-to-moderate severity. Only application-site reactions and breast pain (which increased with dose) were more common with 17β-estradiol than with placebo and considered to be possibly – or probably – related to the study medication. There were no other relevant differences in the incidences of adverse events between the treatment groups. The incidence of adverse events resulting in premature withdrawal from treatment was similar in all the treatment groups.

In summary, this study demonstrates that the Menorest matrix system of transdermal 17β-estradiol is effective and well tolerated at dosages between 25 and 75 μg/day in the prevention of bone loss in postmenopausal

women. While 50 μg/day is an appropriate starting dose, a dose of 25 μg/day is an effective option for those women who cannot tolerate higher doses.

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Received for publication 30 June 1998
Accepted in revised form 22 September 1998