Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial

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Summary

Background **Osteoporosis medications increase bone-mineral density (BMD) and lower but do not eliminate fracture risk. The combining of anabolic agents with bisphosphonates has not improved efficacy. We compared combined teriparatide and denosumab with both agents alone.**

Methods **From September, 2009, to January, 2011, we enrolled postmenopausal women with osteoporosis into this randomised, controlled trial. Patients were assigned in a 1:1:1 ratio to receive 20 μg teriparatide daily, 60 mg denosumab every 6 months, or both. BMD was measured at 0, 3, 6, and 12 months. Women who completed at least one study visit after baseline were assessed in a modified intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT00926380.**

Findings **94 (94%) of 100 eligible women completed at least one study visit after baseline. At 12 months, posterior-anterior lumbar spine BMD increased more in the combination group (9·1%, [SD 3·9]) than in the teriparatide (6·2% [4·6], p=0·0139) or denosumab (5·5% [3·3], p=0·0005) groups. Femoral-neck BMD also increased more in the combination group (4·2% [3·0]) than in the teriparatide (0·8% [4·1], p=0·0007) and denosumab (2·1% [3·8], p=0·0238) groups, as did total-hip BMD (combination, 4·9% [2·9]; teriparatide, 0·7% [2·7], p<0·0001; denosumab 2·5% [2·6], p=0·0011).**

Interpretation **Combined teriparatide and denosumab increased BMD more than either agent alone and more than has been reported with approved therapies. Combination treatment might, therefore, be useful to treat patients at high risk of fracture.**

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Introduction

Therapeutic options for osteoporosis have greatly expanded over the past few decades. The introduction of nitrogen-containing bisphosphonates, which act by suppressing bone resorption, has been an important advance.[1–4] Parathyroid hormone (PTH) and teriparatide also help to prevent fractures, but are generally reserved for patients with severe disease because of multiple factors, including cost and the inconvenience of daily injections.[5] The approval of denosumab has further expanded treatment options.[6] Denosumab is a monoclonal antibody that potently blocks the binding of RANKL to its osteoclast-derived receptor (RANK), an interaction that is required for osteoclast formation, activation, and survival.[7] By blocking this receptor binding, denosumab potently inhibits osteoclast-mediated bone resorption. This mechanism differs from that of amino bisphosphonates, which act via inhibition of the enzyme farnesyl pyrophosphate synthase, leading to decreased osteoclast activity and increased osteoclast apoptosis.[8] Despite these advances, no currently approved therapy restores normal bone integrity in most patients with established osteoporosis, and options for those with severe osteoporosis remain limited.

Efforts to improve treatment efficacy by combining osteoporosis medications have been largely unsuccessful. Studies combining PTH or teriparatide and bisphosphonates have reported no benefit compared with PTH or teriparatide alone.[9–12] The pharmacological reasons for the lack of additive effects, however, remain unknown. Animal studies of combined RANKL inhibitors and teriparatide have yielded conflicting results. An early study done in rats suggested that the combination of teriparatide and osteoprotegerin, an endogenous molecule that blocks RANKL binding to RANK, increased bone-mineral density (BMD) and bone strength more than either agent individually, but this finding could not be consistently reproduced.[13–15] To test the hypothesis that combined teriparatide and denosumab would have additive effects on BMD in human beings, we performed a randomised, controlled trial in postmenopausal women with osteoporosis.

Methods

Participants

Women aged 45 years or older were recruited to this open-label randomised, controlled trial from September, 2009, to January, 2011, through targeted mailings,

advertisements, and referrals to Massachusetts General Hospital in Boston, MA, USA. Inclusion criteria were age over 45 years with at least 36 months since the last menses (or hysterectomy with a concentration of follicle-stimulating hormone in serum of 40 IU/L or higher) and a high risk of fracture. We defined high fracture risk according to the following criteria: T score –2·5 or less at the spine, hip, or femoral neck; T score –2·0 or less with at least one BMD-independent risk factor (fracture after age 50 years, parental hip fracture after age 50 years, previous hyperthyroidism, inability to get up from a chair with arms raised, or current smoking);[16] or T score –1·0 or less with history of fragility fracture. The exclusion criteria were hypercalcaemia; hyperparathyroidism; 25-hydroxyvitamin D concentration in serum lower than 50 nmol/L; congenital or acquired bone disease; anaemia; history of malignant disease or radiation therapy; severe cardiopulmonary, liver, renal, or major psychiatric disease; and excessive alcohol intake. Women who had taken glucocorticoids or oral bisphosphonates within 6 months before enrolment, oestrogen, selective oestrogen-receptor modulators, or calcitonin within 3 months before enrolment, or who had ever received intravenous bisphosphonates, teriparatide, PTH, or strontium ranelate were also excluded. All women provided written informed consent. The study was approved by the Partners Healthcare Institutional Review Board.

Randomisation and masking

Before randomisation, women were stratified for age (younger than 65 years *vs* 65 years or older) and previous bisphosphonate use. Women were assigned to receive 20 µg teriparatide subcutaneously per day, 60 mg denosumab subcutaneously every 6 months, or both, for 12 months. Randomisation was done on a 1:1:1 basis in random blocks of three or six created with a computer algorithm. The study medications were dispensed by an independent pharmacy. Physicians interpreting BMD assessments and the laboratory staff doing bone-marker assays were unaware of patients' treatment groups.

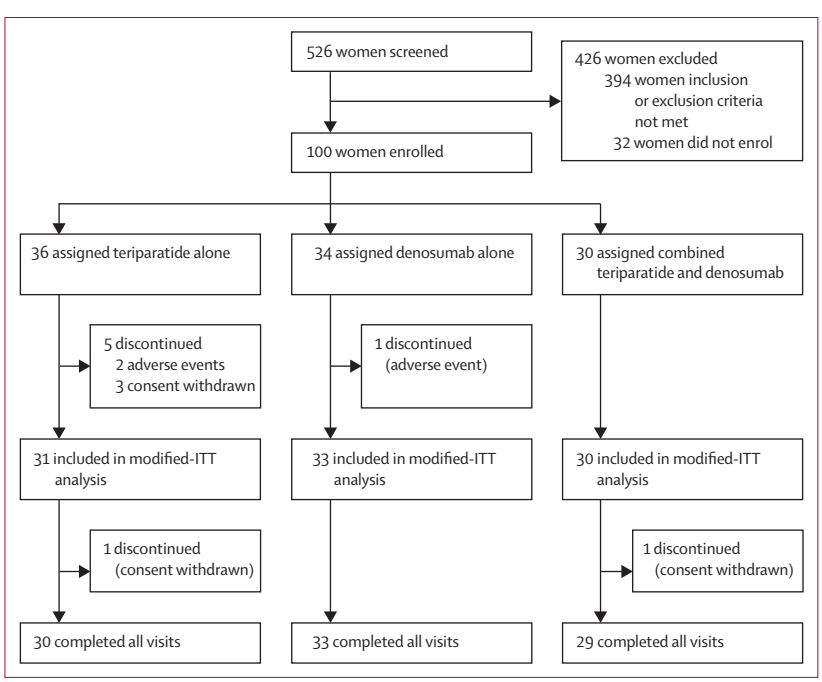


Figure 1: **Trial profile**
ITT=intention to treat.

Study assessments

Women attended Massachusetts General Hospital at 0, 3, 6, and 12 months for collection of morning fasting blood samples (collected 24 h after last injection in women taking teriparatide) and assessment by dual energy x-ray absorptiometry (DXA). High-resolution peripheral quantitative CT was also done at each visit but findings will be reported separately. Adherence to teriparatide was assessed by diary. Women were asked to complete a food-frequency questionnaire developed by the study investigators, in an interview at baseline, to assess calcium intake. Calcium and vitamin D were prescribed to achieve total daily intakes of 1200 mg calcium and 25-hydroxyvitamin D concentrations in serum greater than 50 nmol/L.

A Hologic QDR 4500A densitometer (Hologic, Waltham, MA, USA) was used to assess areal BMD of the posterior-anterior lumbar spine (PA spine), total hip, femoral neck, and distal third of the radial shaft. Each woman's BMD was measured on the same densitometer at all visits. The SD values for in-vivo reproducibility of measurements are 0·005 g/cm² for PA spine, 0·006 g/cm² for total hip, and 0·007 g/cm² for femoral neck. In the study centre, the least significant changes are 0·0157 g/cm², 0·0183 g/cm², and 0·0187 g/cm², respectively. Quality-control measurements were made daily with a Hologic anthropomorphic spine phantom (Hologic). Vertebrae in which obvious deformities or focal sclerosis were detected were excluded.

Serum samples were stored at –70°C until the end of the study when biomarkers of bone turnover (osteocalcin and PINP for bone formation, and β-CTX for bone resorption) were assessed. Osteocalcin was measured by electrochemiluminescent immunoassay (Meso Scale Discovery, Rockville, MD, USA), with interassay and intra-assay coefficients of variation of 10% and 8%, respectively. PINP was measured by radioimmunoassay (Orion Diagnostica, Espoo, Finland), with interassay and intra-assay coefficients of variation of 6–10% and 7–10%, respectively. β-CTX was measured with double-antibody ELISA (Roche Diagnostics, Indianapolis, IN, USA) with interassay and intra-assay coefficients of variation of 2–6% and 1–5%, respectively.

Safety and tolerability

Safety and tolerability were assessed by study physicians at each study visit. Whether adverse effects were related

to the study drug was assessed by a study physician at the time of reporting of each event.

Statistical analysis

We used a modified intention-to-treat analysis, which included all data from women who completed at least one study visit after baseline. Statistical analyses were done with SAS for Windows (version 9.1). The predetermined primary endpoint was the percentage change from baseline in PA spine BMD at 12 months. We compared mean percentage changes in the combination group with those in the single-therapy groups. Secondary endpoints were percentage changes from baseline in BMD of total hip, femoral neck, and distal one-third of the radius shaft, overall changes in osteocalcin, PINP, and β-CTX concentrations at 12 months, differences between groups in each variable at 3 and 6 months, and changes within groups from baseline to each follow-up visit.

Data are presented as mean (SD) unless otherwise specified. Baseline characteristics and differences between groups in mean BMD changes at 12 months were compared with one-way ANOVA. Differences between groups were confirmed by independent *t* test with Bonferroni correction for multiple comparisons. To investigate differences between groups in percentage changes of bone-turnover biomarkers, we calculated the mean net area under the curve (AUC) from the baseline to 12 months. Once the AUC was determined, we subtracted the area of the rectangle defined by the projected baseline value over the time period. Between-group differences in net AUCs were compared by one-way ANOVA and independent *t* test with Bonferroni correction for multiple comparisons. Within-group changes from baseline were assessed by paired *t* test.

Two-sided p values of 0·05 or less were taken to be significant. Unadjusted p values are reported, and adjusted p values are also reported when Bonferroni correction resulted in a change in significance. Estimates of the expected treatment effects and SD were obtained from previous studies done at our institution.[9] On the basis of an SD of 2·5% and a sample size of 25 women in each group, we calculated that the study had 80% power to detect at least a 3% difference in PA spine BMD. This study is registered with ClinicalTrials.gov, number NCT00926380.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

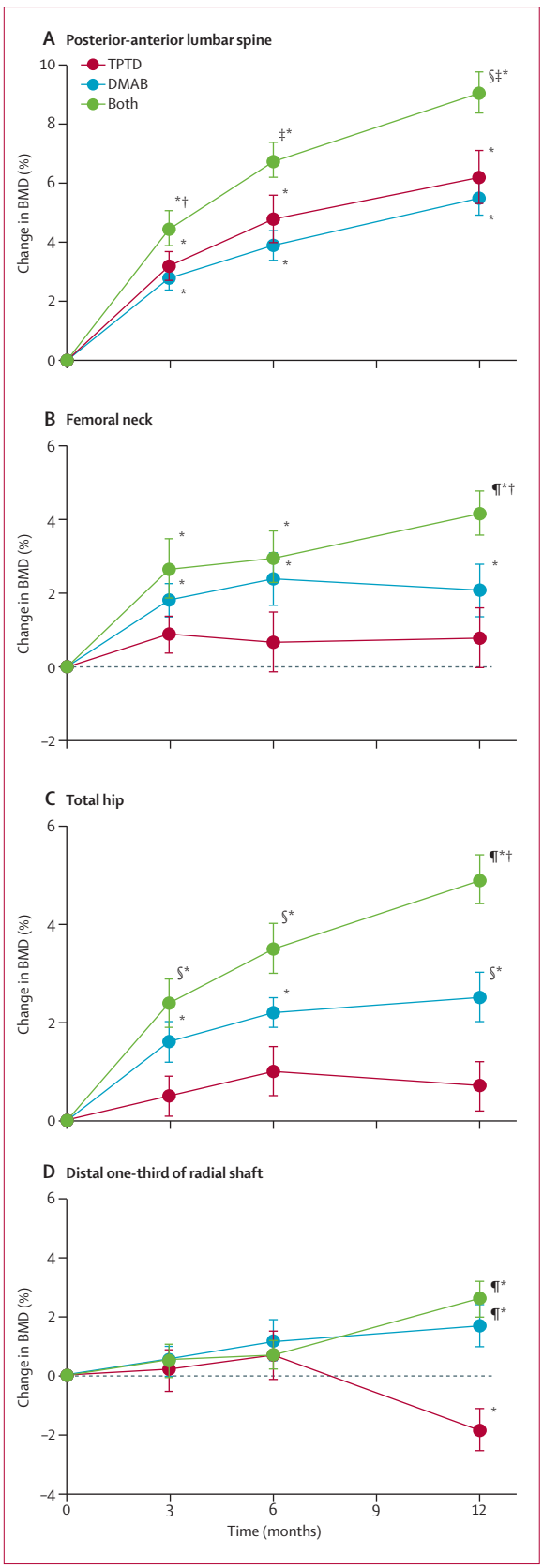
Of the 100 women enrolled, six did not complete a visit after baseline and, therefore, 94 (94%) were included in this analysis (figure 1). Two additional women discontinued the study after completing at least one post-baseline visit. Of the eight women who did not complete all study visits, three withdrew for personal reasons (two in the teriparatide group and one in the combination-therapy group). Five women discontinued for medical reasons, four in the teriparatide group (rash n=1, nausea n=1, irritability n=1, and exacerbation of chronic obstructive pulmonary disease n=1) and one in the denosumab group (breast cancer). Baseline characteristics were similar across all groups (table 1). All women in the combination-therapy group and 29 (94%) of 31 in the teriparatide group reported taking at least 85% of teriparatide doses. All women in the denosumab and combination-therapy groups received all expected denosumab doses. Individual vertebra with obvious deformities or focal sclerosis were removed from the PA spine analysis.

After 12 months of treatment, mean PA spine BMD had increased significantly in all treatment groups (p<0·0001), but increased significantly more in the combination-therapy group than in the teriparatide (p=0·0139) or denosumab (p=0·0005) groups (figure 2, table 2). Increase in BMD of the PA spine did not differ significantly between the teriparatide and denosumab groups (p=0·5346).

	Teriparatide group (n=31)	Denosumab group (n=33)	Combination therapy group (n=30)
Age (years)	65·5 (7·9)	66·3 (8·3)	65·9 (9·0)
Height (cm)	160·3 (7·2)	161·6 (6·8)	159·3 (5·8)
Body-mass index (kg/m²)	25·5 (3·8)	24·1 (3·9)	25·4 (4·9)
White, non-Hispanic	31 (100%)	30 (91%)	27 (90%)
History of fragility fracture	16 (52%)	12 (36%)	10 (33%)
Previous oral bisphosphonate use	13 (42%)	12 (36%)	10 (33%)
Duration of use (months)	40 (25)	43 (27)	28 (21)
Time since discontinuation (months)	27 (20)	36 (23)	42 (17)
25(OH)D concentration in serum (nmol/L)	77·8 (21·1)	88·2 (26·3)	84·6 (30·0)
Alkaline phosphatase concentration in serum (U/L)	75·8 (16·8)	78·8 (16·8)	84·2 (20·8)
Osteocalcin (ng/mL)	49·0 (28·8)	42·9 (19·4)	52·2 (29·9)
PINP (μg/L)	46·6 (19·9)	45·7 (16·7)	49·3 (20·9)
β-CTX (ng/mL)	0·36 (0·15)	0·39 (0·21)	0·43 (0·17)
DXA BMD (g/cm²)			
Posterior-anterior lumbar spine	0·823 (0·111)	0·866 (0·088)	0·856 (0·131)
Femoral neck	0·643 (0·061)	0·641 (0·086)	0·642 (0·067)
Total hip	0·757 (0·068)	0·766 (0·100)	0·759 (0·073)
Distal one-third of the radius shaft	0·612 (0·069)	0·602 (0·082)	0·613 (0·070)
T score			
Posterior-anterior lumbar spine	–2·0 (1·0)	–1·6 (0·8)	–1·8 (1·4)
Femoral neck	–1·9 (0·5)	–1·9 (0·8)	–1·9 (0·6)
Total hip	–1·5 (0·6)	–1·5 (0·8)	–1·5 (0·6)
Distal one-third of the radius shaft	–1·4 (1·1)	–1·5 (1·4)	–1·3 (1·2)

Data are mean (SD) or number (%). 25(OH)D=25-hydroxyvitamin D. DXA=dual x-ray absorptiometry. BMD=bone-mineral density.

Table 1: **Baseline characteristics of women included in the modified-intention-to-treat analysis**



See Online for appendix

***Figure 2*: Mean (SE) percentage changes in bone-mineral density**
(A) Posterior-anterior lumbar spine. (B) Femoral neck. (C) Total hip. (D) Distal one-third of the radial shaft. *p<0·05 *vs* baseline. †p<0·05 *vs* denosumab alone. ‡p<0·001 *vs* denosumab alone. §p<0·05 *vs* teriparatide alone. ¶p<0·001 *vs* teriparatide alone. TPTD=teriparatide. DMAB=denosumab. BMD=bone-mineral density.

Mean femoral-neck BMD had increased significantly at 12 months compared with baseline in the denosumab and combination-therapy groups (p=0·0034 and p<0·0001, respectively), but not in the teriparatide group (p=0·2929). Femoral-neck BMD increased more in women who received combination therapy than in those who received denosumab alone (p=0·0238) or teriparatide alone (p=0·0007; figure 2, table 2). The changes in femoral-neck BMD did not differ significantly between the teriparatide and denosumab groups (p=0·1939).

Mean total-hip BMD had also increased at 12 months in the denosumab and combination-therapy groups (both p<0·0001), but not in the teriparatide group (p=0·1599). Total-hip BMD increased more in the combination-therapy group than in the denosumab group (p=0·0011) and the teriparatide group (p<0·0001; figure 2, table 2). Mean total-hip BMD increased more in the denosumab group than in the teriparatide group (p=0·0097).

We found no differences in changes in BMD between the combination-therapy and denosumab groups in the distal one-third of the radial shaft BMD (p=0·3100), but both groups differed when compared with the teriparatide group (p=0·0009 *vs* denosumab, p<0·0001 *vs* combination therapy; figure 2, table 2).

In women treated with teriparatide alone, mean serum osteocalcin, PINP, and β-CTX concentrations in serum increased significantly compared with baseline at all timepoints (figure 3, appendix) and were significantly greater than the corresponding means in the other two groups (p<0·0001 for all within-group and between-group comparisons). The net AUC for each marker was also greater for women treated with teriparatide than were those for women treated with either denosumab or combination therapy (p<0·0001 for all comparisons).

In the denosumab group, mean serum osteocalcin concentration decreased between baseline and all timepoints (p<0·0001 for all within-group comparisons). In the combination group, mean osteocalcin concentration remained similar to baseline at 3 months (p=0·8644) but had decreased significantly at months 6 (p=0·0244) and 12 (p<0·0001). The net AUC for mean osteocalcin was suppressed more in the denosumab group than in the combination-therapy group (p=0·0002), and the mean osteocalcin concentrations in the denosumab group were lower than in the combination-therapy group at all individual timepoints (p<0·0001 at 3 months, p=0·0016 at 6 months, and p=0·0018 at 12 months).

Mean PINP concentration in serum decreased significantly from baseline at all timepoints in the denosumab and combination-therapy groups (p<0·0001 for all within-group comparisons). The reduction in mean PINP concentration was greater in the denosumab group than the combination-therapy group at 3 months (p=0·0003) and 6 months (p=0·0432), although the latter comparison was no longer significant after Bonferroni adjustment (p=0·0864). Mean PINP concentrations at 12 months did not differ between the denosumab and combination

	Mean (SD) 12-month percentage change in BMD (%)			Mean (95% CI) percentage differences between groups	
	Teriparatide group (%)	Denosumab group (%)	Combination-therapy group (%)	Combination *vs* teriparatide	Combination *vs* denosumab
Posterior-anterior lumbar spine	6·2 (4·6)	5·5 (3·3)	9·1 (3·9)	2·9 (0·6–5·1)	3·5 (1·6–5·4)
Femoral neck	0·8 (4·1)	2·1 (3·8)	4·2 (3·0)	3·4 (1·5–5·3)	2·1 (0·3–3·8)
Total hip	0·7 (2·7)	2·5 (2·6)	4·9 (2·9)	4·2 (2·8–5·6)	2·4 (1·0–3·8)
Distal one-third radius shaft	−1·8 (3·6)	1·7 (3·2)	2·6 (2·9)	4·3 (2·5–6·2)	0·9 (0·9–2·6)

BMD=bone-mineral density.

***Table 2*: Changes in bone-mineral density and differences between groups at 12 months**

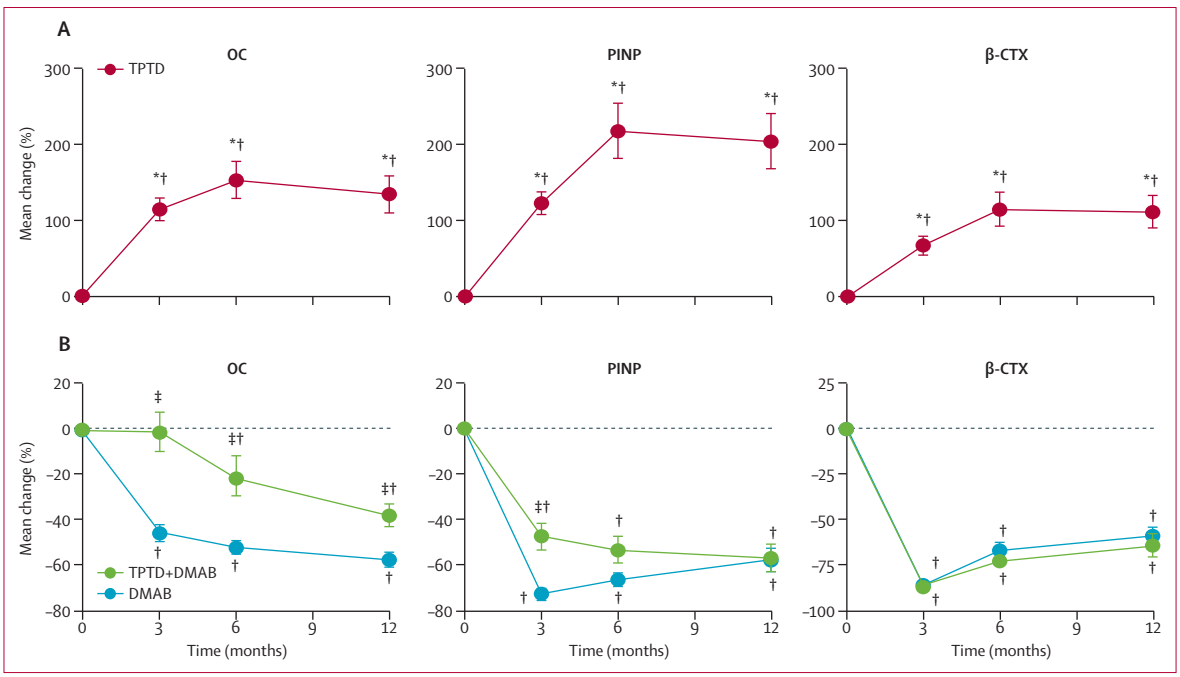


***Figure 3*: Mean (SE) percentage changes in bone-turnover markers**

(A) Teriparatide. (B) Denosumab alone and teriparatide and denosumab combined. Data for the teriparatide-alone group are shown separately for clarity. *p<0·001 *vs* denosumab and *vs* combined therapy. †p<0·05 *vs* baseline. ‡p<0·01 *vs* denosumab. TPTD=teriparatide. OC=osteocalcin. DMAB=denosumab.

groups (p=0·9754). The decrease in net AUC was greater in the denosumab group than the combination-therapy group before adjustment (p=0·0390), but after adjustment this difference was no longer significant (p=0·0780).

In the denosumab and combination-therapy groups, mean concentrations of β-CTX in serum were significantly lower than at baseline at all timepoints (p<0·0001 for all within-group comparisons). Both the net AUC and degree of suppression at each timepoint were similar in these two groups.

No women developed hypocalcaemia. Mild asymptomatic hypercalcaemia, defined as 2·7 mmol/L calcium in serum, was detected in one woman in the teriparatide group, one in the denosumab group, and three in the combination-therapy group.

Serious adverse events in the teriparatide group were non-ST-segment-elevation myocardial infarction, hyperglycaemia requiring admission to hospital in a patient with diabetes, and breast cancer detected by routine screening mammography shortly before the woman's 12-month visit. In the denosumab group, one woman was diagnosed with breast cancer after routine screening mammography 6 weeks after starting the study. In the combination-therapy group, one patient had an exacerbation of asthma that required admission to hospital and another patient was diagnosed as having melanoma shortly before her 12-month visit. All serious adverse events were judged unrelated to the study treatments.

Discussion

In this 12-month randomised, controlled trial we show that combined teriparatide and denosumab increased BMD at the PA spine, femoral neck, and hip significantly more than either drug alone (panel). These additive effects were, therefore, seen in sites of both trabecular and mixed cortical and trabecular bone. Moreover, the

Panel: **Research in context**

Systematic review

We searched PubMed with the terms "anabolic", "antiresorptive", "osteoporosis", and "combination therapy". No parameters were set for language or date of publication. We reviewed all randomised, controlled trials as well as pertinent animal studies published in peer-reviewed journals.

Interpretation

Combined teriparatide and denosumab increased bone-mineral density at the spine and hip more than either drug alone in postmenopausal women with osteoporosis. Thus, the combination of these anabolic and antiresorptive treatments might have important therapeutic implications in the treatment of women at especially high risk of fracture.

12-month changes in femoral-neck and total-hip BMD in the combination-therapy group (4·2% and 4·9%, respectively) were greater than have been reported with approved therapies for postmenopausal osteoporosis.[1–6]

Our findings are in contrast to those of previous trials that assessed the effect of bisphosphonates combined with teriparatide or PTH. In randomised controlled trials of postmenopausal women who received alendronic acid and teriparatide or PTH for various durations, efficacy did not differ between the combination-therapy and individual-therapy groups.[9–11] Similarly, combined teriparatide and zoledronic acid given for 12 months was not associated with better results than each drug individually.[12] In a study in which alendronic acid was added to previously started teriparatide therapy, however, the results were more promising.[17]

Direct comparison of the findings from bisphosphonate trials with those of this study is limited by differences in study design and treatment doses. Nonetheless, the outcomes with regimens that contain bisphosphonates seem to differ substantially from those we found with the combination of teriparatide and denosumab. The mechanisms underlying these differences are unclear, but the larger increases in BMD we found might be at least partly explained by net effects on osteoclast function. Combined teriparatide and denosumab was associated with acute and sustained suppression of bone resorption, as shown by substantial decreases in mean β-CTX concentrations, that was similar to the suppression seen in the group treated with denosumab alone. By contrast, in trials of bisphosphonate-based regimens bisphosphonates alone suppressed bone resorption more than combination therapy. Specifically, combined zoledronic acid and teriparatide suppressed the mean concentration of β-CTX in serum only transiently, and combined alendronic acid and teriparatide or PTH suppressed bone resorption significantly less than alendronic acid alone.[10–12,18] Bone formation in this study, as assessed by measurement of osteocalcin and PINP, was suppressed less in women who received combination therapy than in those who received denosumab alone. This finding is qualitatively similar to those reported in trials of bisphosphonate-based regimens.[10–12,18]

Our results show that denosumab, unlike bisphosphonates, is associated with maximum suppression of bone resorption, even when given with teriparatide. At the same time, measurable levels of bone formation were sustained in women who received combined teriparatide and denosumab, even in the setting of substantial osteoclast inhibition. Together, these data suggest that accelerated bone resorption is not required for teriparatide to exert at least some effect on osteoblasts. This property of teriparatide is in contrast to what has previously been suggested.[18,19] Thus, the combination of denosumab and teriparatide seems to unlink more effectively bone resorption and formation than the combination of bisphosphonates and PTH. Perhaps, unlike bisphosphonate combinations, the combination of teriparatide and denosumab permits continued teriparatide-induced modelling-based bone formation, as has been documented in some studies of teriparatide monotherapy.[20]

Animal studies provide some insight into the unique effects of combining denosumab and teriparatide. In rats combined osteoprotegerin and teriparatide increased BMD and bone strength more than either treatment alone.[13] Histomorphometric analysis showed that osteoclast numbers in rats that received this treatment were similar to those in rats treated with osteoprotegerin alone, whereas the osteoblast numbers were similar to those in rats treated with teriparatide alone.[13] These histomorphometric observations are consistent with the changes in biochemical markers of bone turnover we found in our human study. Additionally, in mice in which both alleles of the gene that encodes RANK (*TNFRSF11A*) have been inactivated, and hence completely lack osteoclasts, PTH-stimulated osteoblastic bone formation still occurs.[14] These findings support those in our study and strongly suggest that osteoclast activation via RANKL is not required for at least some of teriparatide's action to increase bone formation.

This study has some potential limitations. First, although we report clinically meaningful differences in BMD between groups, the study was not powered to detect effects on fracture risk. Nonetheless, DXA-derived BMD is a well validated surrogate endpoint in osteoporosis studies and correlates well with fracture risk.[21,22] Additionally, while the baseline frequency of previous bisphosphonate use and fragility fracture was not significantly different between treatment groups, a numerically greater number of women with previous bisphosphonate use and previous fractures were randomised to the teriparatide group. Nevertheless, responses to therapy did not differ between women with and without fractures or with and without history of bisphosphonate exposure, overall or within groups. Another potential

limitation is the open-label design. Because the physicians who interpreted the DXA measurements and the laboratory staff who did the bone-marker assays were unaware of patients' treatment allocation, however, bias is unlikely. The generalisability of our results must be assessed in the context of our study population, which was recruited from one metropolitan area and was mostly white. Changes in BMD in the single-therapy groups, however, are similar to those reported in large multicentre and multinational studies.[5,6] Finally, although the safety profile of the combined therapy seems to be similar to the profiles in the single-therapy groups, this study could not adequately assess the long-term safety of any of the interventions. To do so would require a much larger clinical trial.

Combined teriparatide and denosumab increases BMD at the spine, hip, and femoral neck in postmenopausal women with osteoporosis more than either agent alone. Moreover, the BMD changes in the combined-therapy group were greater than have been reported with any approved therapies. Although studies are needed to assess reductions in fracture risk and to explore the effects of different doses and durations of treatment, the results of this trial suggest that this specific combination of drugs could be a useful option in the treatment of patients with osteoporosis at especially high risk of fracture.

Contributors

HL, S-AMB-B, RMN, and BZL conceived and designed the study. RK, ES-S, EAMcK, S-AMB-B, RMN, and BZL enrolled the patients. JNT, AVU, RK, ES-S, S-AMB-B, RMN, and BZL were involved in data acquisition, analysis, and interpretation. HL designed and did the statistical analyses with input from RMN and BZL. JNT and AVU wrote the first draft of the report. All authors edited and approved the report for final submission.

Conflicts of Interest

RMN is a consultant for Eli Lilly and BZL was previously a consultant for Amgen Inc. All authors receive or have received research funding from Amgen and Eli Lilly.

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