Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial

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Summary

Background Unlike most chronic diseases, osteoporosis treatments are generally limited to a single drug at a fixed dose and frequency. Nonetheless, no approved therapy is able to restore skeletal integrity in most osteoporotic patients and the long-term use of osteoporosis drugs is controversial. Thus, many patients are treated with the sequential use of two or more therapies. The DATA study showed that combined teriparatide and denosumab increased bone mineral density more than either drug alone. Discontinuing teriparatide and denosumab, however, results in rapidly declining bone mineral density. In this DATA-Switch study, we aimed to assess the changes in bone mineral density in postmenopausal osteoporotic women who transitioned between treatments.

Methods This randomised controlled trial (DATA-Switch) is a preplanned extension of the denosumab and teriparatide administration study (DATA), in which 94 postmenopausal osteoporotic women were randomly assigned to receive 24 months of teriparatide (20 mg daily), denosumab (60 mg every 6 months), or both drugs. In DATA-Switch, women originally assigned to teriparatide received denosumab (teriparatide to denosumab group), those originally assigned to denosumab received teriparatide (denosumab to teriparatide group), and those originally assigned to both received an additional 24 months of denosumab alone (combination to denosumab group). Bone mineral density at the spine, hip, and wrist were measured 6 months, 12 months, 18 months, and 24 months after the drug transitions as were biochemical markers of bone turnover. The primary endpoint was the percent change in posterior-anterior spine bone mineral density over 4 years. Between-group changes were assessed by one-way analysis of variance in our modified intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00926380.

Findings Between Sept 27, 2011, and Jan 28, 2013, eligible women from the DATA study were enrolled into DATA-Switch. Of 83 potential enrollees from the DATA study, 77 completed at least one post-baseline visit. After 48 months, the primary outcome of mean spine bone mineral density increased by 18·3% (95% CI 14·9–21·8) in 27 women in the teriparatide to denosumab group, 14·0% (10·9–17·2) in 27 women the denosumab to teriparatide group, and 16·0% (14·0–18·0) in 23 women in the combination to denosumab group, although this increase did not differ significantly between groups (for between-group comparisons, p=0·13 for the teriparatide to denosumab group *vs* the denosumab to teriparatide group, p=0·30 for the teriparatide to denosumab group *vs* the combination to denosumab group, and p=0·41 for the denosumab to teriparatide group *vs* the combination to denosumab group). For the bone mineral density secondary outcomes, total hip bone mineral density increased more in the teriparatide to denosumab group (6·6% [95% CI 5·3–7·9]) than in the denosumab to teriparatide group (2·8% [1·3–4·2], p=0·0002), but had the greatest increase in the combination to denosumab group (8·6% [7·1–10·0]; p=0·0446 *vs* the teriparatide to denosumab group, p<0·0001 *vs* the denosumab to teriparatide group). Similarly, femoral neck bone mineral density increased more in the teriparatide to denosumab group (8·3% [95% CI 6·1–10·5]) and the combination to denosumab group (9·1% [6·1–12·0]) than in the denosumab to teriparatide group (4·9% [2·2–7·5]; p=0·0447 for teriparatide to denosumab *vs* denosumab to teriparatide, p=0·0336 for combination to denosumab *vs* denosumab to teriparatide). Differences between the combination to denosumab group and the teriparatide to denosumab group did not differ significantly (p=0·67). After 48 months, radius bone mineral density was unchanged in the teriparatide to denosumab group (0·0% [95% CI –1·3 to 1·4]), whereas it decreased by –1·8% (–5·0 to 1·3) in the denosumab to teriparatide group, and increased by 2·8% (1·2–4·4) in the combination to denosumab group (p=0·0075 for the teriparatide to denosumab group *vs* the combination to denosumab group; p=0·0099 for the denosumab to teriparatide group *vs* the combination to denosumab group). One participant in the denosumab to teriparatide group had nephrolithiasis, classified as being possibly related to treatment.

Interpretation In postmenopausal osteoporotic women switching from teriparatide to denosumab, bone mineral density continued to increase, whereas switching from denosumab to teriparatide results in progressive or transient bone loss. These results should be considered when choosing the initial and subsequent management of postmenopausal osteoporotic patients.

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Research in context

Evidence before this study

We searched PubMed with the terms "anabolic", antiresorptive", "osteoporosis", "combination therapy", "sequential therapy", "denosumab", "bisphosphonates", and "teriparatide". No parameters were set for language or date of publication. We reviewed all randomised controlled trials and accompanying editorials, when available, and animal studies published in peer-reviewed journals. Several high-quality randomised controlled trials have been done addressing the issue of sequential anabolic and bisphosphonate osteoporosis therapy, but none have addressed the sequential use of denosumab and teriparatide.

Added value of this study

In our current study, we report that in osteoporotic women treated with denosumab for 2 years, switching to teriparatide resulted in transient decreases in bone mineral density of the hip and spine, and progressive bone loss at the distal radius. Conversely, we show that the initial use of teriparatide or combined teriparatide plus denosumab followed by denosumab results in the largest 4-year increases in spine and hip bone mineral density reported in any clinical trial so far. As the first study addressing the issue of sequential therapy with denosumab and teriparatide, these results provide a framework by which physicians can make informed decisions when initiating osteoporosis therapy or transitioning from one drug to another.

Implications of all the evidence

These results, along with previous studies performed with other antiresorptive drugs, indicate that physicians should strongly consider the initial use of anabolic therapy (or combined denosumab and teriparatide) in patients with established osteoporosis. Moreover, these findings provide the scientific rationale for the support of this approach by those responsible for the allocation of health-care resources, especially in patients with severe disease. Future research should focus on the efficacy of these interventions in fracture reduction and the cost-effectiveness of combined and sequential use of denosumab and teriparatide in diverse populations.

Introduction

Osteoporotic fractures, more than 75% of which occur in women, are a major cause of death, disability, and worldwide health-care expenditure.[1,2] Unlike most chronic diseases, approved treatments for osteoporosis are generally limited to the use of one drug at a fixed dose and dosing frequency. Although the therapeutic options in osteoporosis treatment have expanded greatly in the past two decades, no currently approved therapy is able to restore skeletal integrity in most patients with established disease.

Current medications approved to treat postmenopausal osteoporosis can be separated into two categories. The most commonly used drugs are the antiresorptive drugs, a class that includes the nitrogen-containing bisphosphonates and the receptor activator of nuclear factor κB ligand (RANKL) inhibitor, denosumab. Less commonly used and generally reserved for patients with severe and established osteoporosis, is the anabolic drug teriparatide (PTH-1-34). In view of the fact that current recommendations question the long-term use of potent antiresorptive osteoporotic drugs and that use of teriparatide is limited to 18–24 months by regulatory bodies,[3,4] the treatment of patients with established or severe osteoporosis often requires the sequential use of several drugs.

Although denosumab and teriparatide are two of the most potent therapies currently available to physicians,[5] both are associated with abrupt and rapid bone loss when discontinued.[6,7] Whether switching from denosumab to teriparatide or from teriparatide to denosumab can prevent this decline in bone mineral density or further increase bone mass is unknown. In the denosumab and teriparatide administration study of postmenopausal osteoporotic women (DATA), we reported that concurrent denosumab and teriparatide administration increases spine and hip bone mineral density more than either drug alone and to a greater degree than has been achieved with any currently available drug.[8,9] Less positive results have been reported for combinations of teriparatide and bisphosphonates.[10–12] We now test the hypothesis that the transition from teriparatide or combined teriparatide plus denosumab to denosumab monotherapy and the transition from denosumab to teriparatide monotherapy will further increase bone mineral density in postmenopausal osteoporotic women. In so doing, we aimed to provide physicians with the evidence necessary to formulate a rational approach to the sequential and combined use of these medications.

Methods

Study design and participants

In the prospectively planned DATA-Switch study, postmenopausal women aged 45 years or older were recruited through targeted mailings, advertisements, and physician referrals. Participants were required to be at least 36 months beyond their last menses (or 36 months after hysterectomy with a concentration of follicle-stimulating hormone in serum of 40 IU/L or higher) and at high fracture risk. High fracture risk was defined as a bone mineral density T score ≤–2·5 at the spine, hip, or femoral neck; T score ≤–2·0 with at least one bone mineral density independent risk factor (fracture after age 50 years, parental hip fracture after age 50 years, previous hyperthyroidism, inability to rise from a chair with arms elevated, or current smoking),[13] or T score ≤–1·0 with a history of a fragility fracture. Participants were excluded if they had evidence of hyperparathyroidism, vitamin D deficiency (serum level <20 ng/mL), other congenital or acquired bone disease, history of malignancy (with the

exception of non-melanoma skin cancer), history of ionising radiation therapy, significant cardiopulmonary, liver, or renal disease, major psychiatric disease, or excessive alcohol intake. Participants were also excluded if they had ever taken parenteral bisphosphonates, teriparatide, or strontium ranelate. Additionally, participants were excluded if they had taken glucocorticoids or oral bisphosphonates within 6 months of enrolment or if they had taken oestrogen, selective oestrogen receptor modulators, or calcitonin within 3 months of enrolment. All provided written informed consent. The study was approved by the Partners Healthcare Institutional Review Board.

Randomisation and masking

In the DATA study, patients were originally randomly assigned (1:1:1) to receive teriparatide, denosumab, or both. Randomisation was done in random blocks of three or six created with a computer algorithm. Before randomisation, women were stratified for age (younger than 65 years *vs* 65 years or older) and previous bisphosphonate use. Physicians interpreting bone mineral density assessments and assessing all serum markers were masked to treatment group.

Procedures

In the original DATA study, participants received teriparatide 20 µg subcutaneously daily (Forteo, Eli Lilly Inc, Indianapolis, IN, USA), denosumab 60 mg subcutaneously every 6 months (Prolia, Amgen Inc, Thousand Oaks, CA, USA), or both drugs. Participants who completed the 24-month trial were then offered enrolment in the DATA-Switch study as long they continued to meet one of the following three criteria: 1) dual x-ray absorptiometry spine or hip T score <–1·5; 2) dual x-ray absorptiometry spine or hip T score <–1·0 plus one or more of the following risk factors for fracture: fracture after age 50 years, parental hip fracture after age 50 years, previous hyperthyroidism, inability to rise from a chair with one's arms elevated, current tobacco smoker; or 3) history of more than one adult low-trauma fracture with any bone mineral density (low-trauma fracture is defined as a fracture after no trauma or fracture after falling <6 inches when stationary or moving slower than a run).

In DATA-Switch, women originally assigned to 24 months of teriparatide received 24 months of denosumab, whereas those participants who were originally randomised to 24 months of denosumab received 24 months of teriparatide. Participants who originally received both drugs, received an additional 24 months of denosumab alone (figure 1). After the drug transition, participants were seen 1 month later (month 25), and then again at months 30, 36, 42, and 48. At the 25-month visit, participants underwent blood sampling only, whereas at all the other visits blood sampling and dual energy x-ray absorptiometry were done. All blood sampling was done before teriparatide administration (ie, 24 h after the last teriparatide dose) and physicians interpreting bone mineral density assessments were masked to treatment group. All participants were given calcium carbonate and vitamin D supplements if needed to achieve a total daily intake of 1200 mg of elemental calcium and to maintain a serum 25-hydroxyvitamin D level of at least 20 ng/mL. Adherence to teriparatide was assessed by medication diary.

Areal bone mineral density of the posterior-anterior lumbar spine, total hip, femoral neck, and distal 1/3 radius shaft was measured by dual x-ray absorptiometry with a Hologic QDR 4500A densitometer (Hologic, Waltham, MA, USA). All scans of an individual participant were done on the same densitometer. Quality control measurements were done daily with a Hologic anthropomorphic spine phantom. Our standard deviations of in-vivo same-day reproducibility are 0·005 g/cm², 0·006 g/cm², and 0·007 g/cm² for posterior-anterior spine, total hip, and femoral neck bone mineral density measurements, respectively.

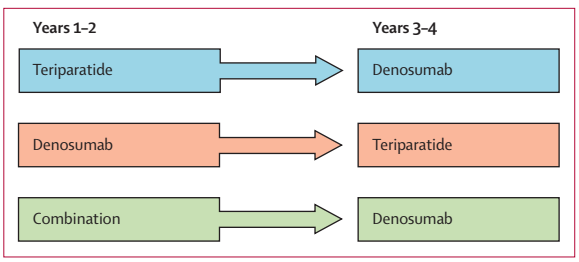

Figure 1: **DATA-Switch study design**

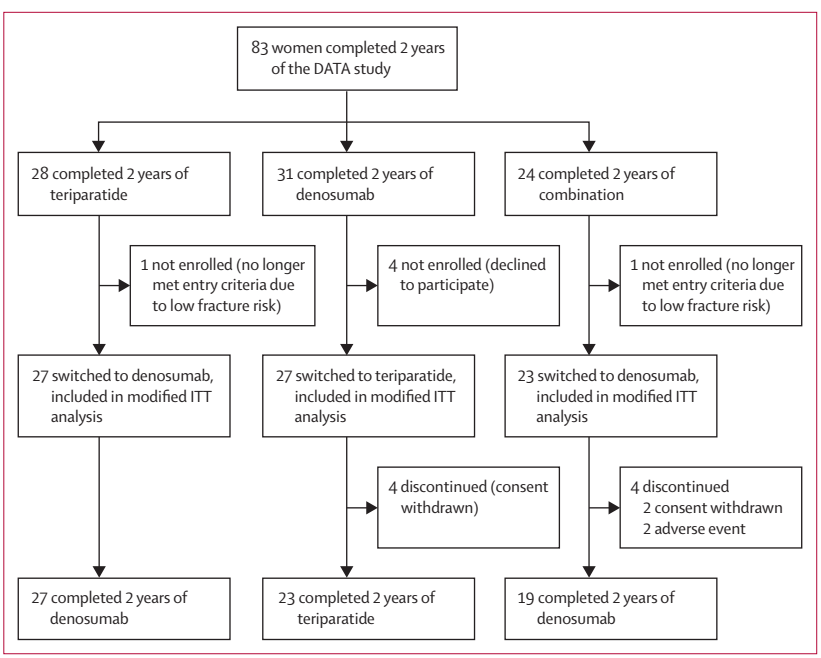

Figure 2: **Trial profile**
ITT=intention to treat.

Fasting morning blood samples (collected 24 h after last injection if taking teriparatide) were obtained at every visit. Serum osteocalcin, a marker of bone formation, was measured via electrochemiluminescent immunoassay (Meso Scale Discovery, Rockville, MD, USA) with interassay and intra-assay coefficients of variation of 10% and 8%, respectively. Serum β-C-terminal telopeptide of type I collagen (C-telopeptide), a marker of bone resorption, was measured via a fully automated electrochemiluminescent immunoassay (Roche Diagnostics, Indianapolis, IN, USA) with an interassay coefficient of variation of less than 5%. The limit of detection for serum C-telopeptide was 0·01 ng/mL and the reportable range was 0·01–5·99 ng/mL. Biochemical markers of bone turnover were only measured in participants completing 48 months of therapy. For every marker, all blood samples from a participant were analysed together in the same assay run.

Study physicians assessed the safety and tolerability of the medications at each visit. At the time of reporting, a study physician also determined whether each adverse event was related to the study drug.

Outcomes

The predetermined primary endpoint was the percent change in posterior-anterior spine bone mineral density over 4 years. Secondary endpoints included the percent change in total hip, femoral neck, and radius shaft bone mineral density and the percent change in serum osteocalcin and C-telopeptide concentrations.

Statistical analysis

For the **WHO Fracture Risk Assessment Tool** see https://www.shef.ac.uk/FRAX/index.aspx

Sample size considerations were reported previously for the 94 participants enrolled in the DATA study.[9] Between-group baseline characteristics of DATA-Switch participants were compared by one-way analysis of variance (ANOVA). For bone mineral density, we used a modified intention-to-treat analysis, which included all data from participants completing at least one additional bone density measurement after switching therapies (month 30). Between-group differences in the mean change in bone mineral density from baseline to 48 months were examined by one-way ANOVA and subsequent between-group differences confirmed by independent samples *t* test. Between-group differences in the percent change in bone mineral density from 24 months to 48 months were also examined by one-way ANOVA and if significant by subsequent between-group differences confirmed by independent samples *t* test. Biochemical markers of bone turnover measurements were restricted to participants who completed all visits (valid completers). Because the changes in these markers were not normally distributed, the medians and 25th–75th percentiles were used for data summary and the between-group differences in each marker at each timepoint was examined by Wilcoxon's rank sum test. Two-sided $p \leq 0 \cdot 05$ was considered statistically significant. Statistical analysis was done with SAS version 9.2.

This study is registered with ClinicalTrials.gov, number NCT00926380.

Role of the funding source

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

Results

Between Sept 27, 2011, and Jan 28, 2013, 77 participants who completed the DATA study were enrolled into DATA-Switch, of whom 27 women originally assigned to 24 months of teriparatide received 24 months of denosumab, 27 women originally randomised to 24 months of denosumab received 24 months of teriparatide, and 23 women who originally received both drugs received an additional 24 months of denosumab alone. 77 participants completed at least one post-baseline visit (modified intention-to-treat population) and 69 completed all visits through to 48 months (figure 2).

Baseline demographic and clinical characteristics did not differ significantly between the three treatment groups (table 1). Additionally, no significant differences in the baseline characteristics of women in the DATA-Switch cohort compared with those in the original DATA population (either within each group or the population as a whole) were noted (data not shown). The entry criteria resulted in mean 10-year fracture risks (based on the WHO Fracture Risk Assessment Tool) of 14·4% and 2·6% for major osteoporotic fracture and hip fracture, respectively. 59% of participants had at least one T score of ≤–2·5.

	Teriparatide to denosumab (N=27)	Denosumab to teriparatide (N=27)	Combination to denosumab (N=23)
Age (years)	66·1 (7·9)	65·1 (6·2)	65·3 (8·0)
Body-mass index (kg/m²)	25·5 (3·7)	23·8 (4·1)	25·9 (5·2)
White, non-Hispanic	27 (100%)	24 (89%)	20 (87%)
Clinical fracture at age >45 years (%)	14 (52%)	10 (37%)	8 (35%)
Previous oral bisphosphonate use (%)	12 (44%)	9 (33%)	9 (39%)
Duration of use (months)	45 (23)	45 (26)	25 (21)
Time since discontinuation (months)	27 (20)	35 (24)	41 (18)
Serum 25-hydroxyvitamin D concentration (ng/mL)	32·2 (8·5)	35·9 (11·0)	34·8 (12·8)
Osteocalcin (ng/mL)	46·3 (26·1)	43·9 (20·2)	55·0 (32·6)
C-terminal telopeptide (ng/mL)	0·34 (0·15)	0·41 (0·22)	0·44 (0·17)
DXA bone mineral density (g/cm²)			
Posterior-anterior spine	0·815 (0·109)	0·863 (0·096)	0·847 (0·130)
Femoral neck	0·642 (0·064)	0·639 (0·090)	0·638 (0·054)
Total hip	0·756 (0·072)	0·759 (0·102)	0·750 (0·068)
One-third radius	0·618 (0·072)	0·608 (0·088)	0·614 (0·072)

Data are mean (SD), unless otherwise noted. DXA=dual x-ray absorptiometry.

Table 1: **Baseline demographic and clinical characteristics**

As reported previously, after 24 months of the originally assigned drugs, mean lumbar spine bone mineral density had increased significantly in all treatment groups relative to baseline with the greatest increases in women treated with both drugs together.[8] In women switching from teriparatide to denosumab, mean (SD) lumbar spine bone mineral density continued to increase resulting in 48-month increases of 18·3% (8·5). In women switching from combination therapy to denosumab, the net 48-month increase in bone mineral density was 16·0% (4·1; figure 3, table 2). Conversely, in women who after 24 months of denosumab were treated with 24-month teriparatide, lumbar spine bone mineral density decreased over the first 6 months followed by increases resulting in a mean net 48-month increase of 14·0% (6·7). There was no significant difference in the 48-month increase in lumbar spine bone mineral density between any of the treatment groups (primary endpoint): p=0·13 for the teriparatide to denosumab group versus the denosumab to teriparatide group, p=0·30 for the teriparatide to denosumab group versus the combination to denosumab group, and p=0·41 for the denosumab to teriparatide group versus the combination to denosumab group. Bone mineral density increased more after the treatment transition (between months 24 and 48) in the teriparatide to denosumab group (8·6 [SD 5·0]) than in either the denosumab to teriparatide group (4·8 [5·6]; between group p=0·0203) or the combination to denosumab group (3·4 [3·5]; between-group p=0·0005).

Also as reported previously, after 24 months of the originally assigned therapy, mean total hip bone mineral density increased significantly in all treatment groups relative to baseline with the greatest increases in women treated with both drugs.[8] In women switching from teriparatide to denosumab, total hip bone mineral density continued to increase, resulting in 48-month increases of 6·6% (SD 3·3). In women switching from combination therapy to denosumab, total hip bone mineral density also increased. resulting in 48-month net increases of 8·6% (SD 3·0). Conversely, in women who were treated with 24 months of denosumab followed by 24 months of teriparatide, total hip bone mineral density progressively decreased from 24 months to 36 months before beginning to increase between 36 months and 42 months. At the conclusion of DATA-Switch (month 48), total hip bone mineral density had increased more in the combination to denosumab group than in either the teriparatide to denosumab group (between-group

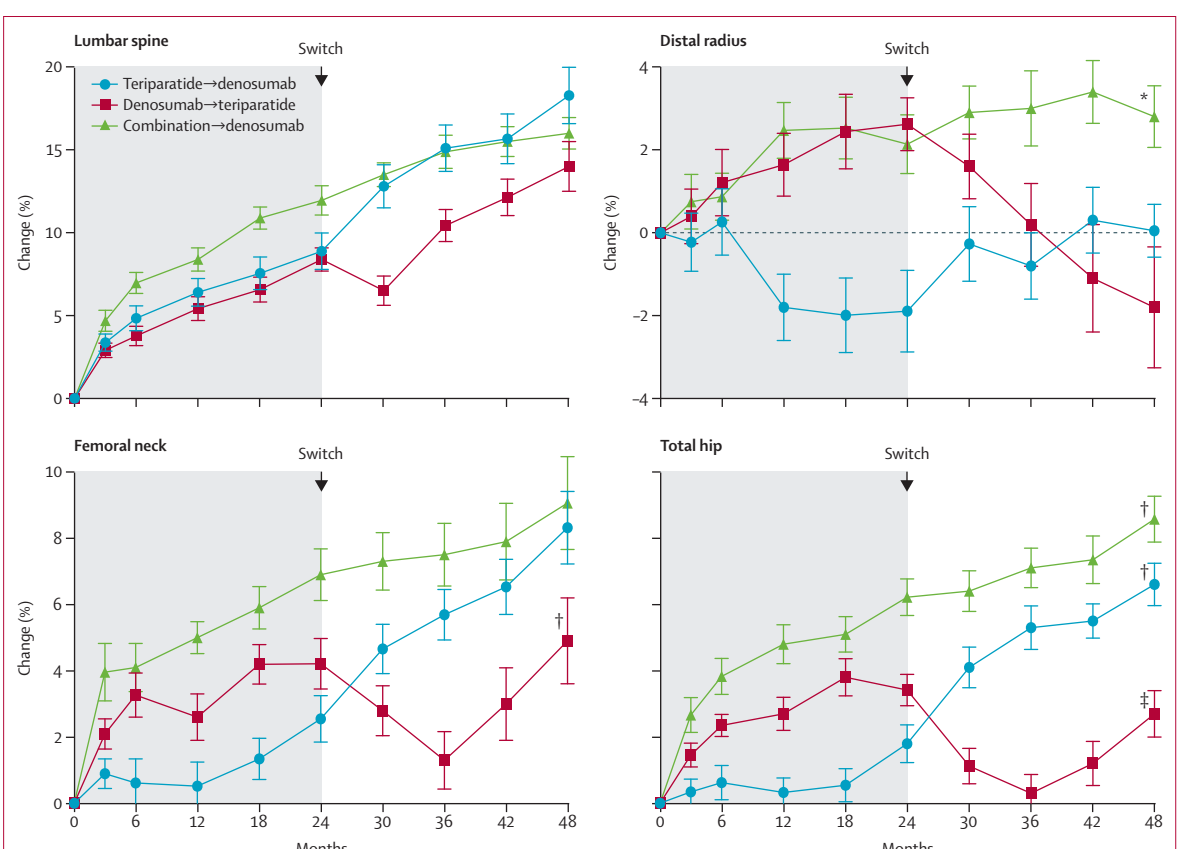

Figure 3: **Mean percent change (SEM; error bars) in bone mineral density from baseline to 48 months in the lumbar spine, 1/3 distal radius, femoral neck, and total hip**

*p<0·01 versus both other groups. †p<0·05 versus both other groups. ‡p<0·0005 versus both other groups.

p=0·0446) or the denosumab to teriparatide group (between-group p<0·0001). At the conclusion of DATA-Switch, total hip bone mineral density also increased more in the teriparatide to denosumab group than in the denosumab to teriparatide group (between-group p=0·0002). When the analysis was restricted to changes occurring after the treatment transitions (months 24–48), total hip bone mineral density increased more in the teriparatide to denosumab group (4·7% [SD 2·6]) than in both the combination to denosumab group (2·2% [1·8]; p=0·0008) and the denosumab to teriparatide group (–0·7% [3·1]; p<0·0001).

Changes in femoral neck bone mineral density after 24 months of the originally assigned therapy showed a pattern similar to total hip, with similar transient bone loss occurring between months 24–36 in women treated with denosumab followed by teriparatide. From 0–48 months, femoral neck bone mineral density increased by 8·3% (SD 5·6) in the teriparatide to denosumab group, 4·9% (6·0) in the denosumab to teriparatide group, and 9·1% (6·1) in the combination to denosumab group (denosumab to teriparatide *vs* teriparatide to denosumab p=0·0447; denosumab to teriparatide *vs* combination to denosumab p=0·0336). However, when the analysis was restricted to changes occurring after the treatment transitions (months 24–48), the increases in the teriparatide to denosumab group

	Teriparatide to denosumab group	Denosumab to teriparatide group	Combination to denosumab group
Percent change 0–48 months			
Lumbar spine	18·3 (14·9 to 21·8)	14·0 (10·9 to 17·2)	16·0 (14·0 to 18·0)
Femoral neck	8·3 (6·1 to 10·5)	4·9 (2·2 to 7·5)	9·1 (6·1 to 12·0)
Total hip	6·6 (5·3 to 7·9)	2·8 (1·3 to 4·2)	8·6 (7·1 to 10·0)
Distal radius	0·0 (–1·3 to 1·4)	–1·8 (–5·0 to 1·3)	2·8 (1·2 to 4·4)
Percent change 24–48 months			
Lumbar spine	8·6 (6·6 to 10·6)	4·8 (2·2 to 7·4)	3·4 (1·7 to 5·2)
Femoral neck	5·6 (3·9 to 7·2)	1·2 (–1·0 to 3·4)	2·1 (–0·2 to 4·5)
Total hip	4·7 (3·7 to 5·8)	–0·7 (–2·0 to 0·7)	2·2 (1·3 to 3·1)
Distal radius	2·3 (0·5 to 4·1)	–5·0 (–7·5 to –2·6)	0·5 (–0·6 to 1·6)

Data are % change (95% CIs).

Table 2: **Mean change in bone mineral density between 0–48 months and 24–48 months**

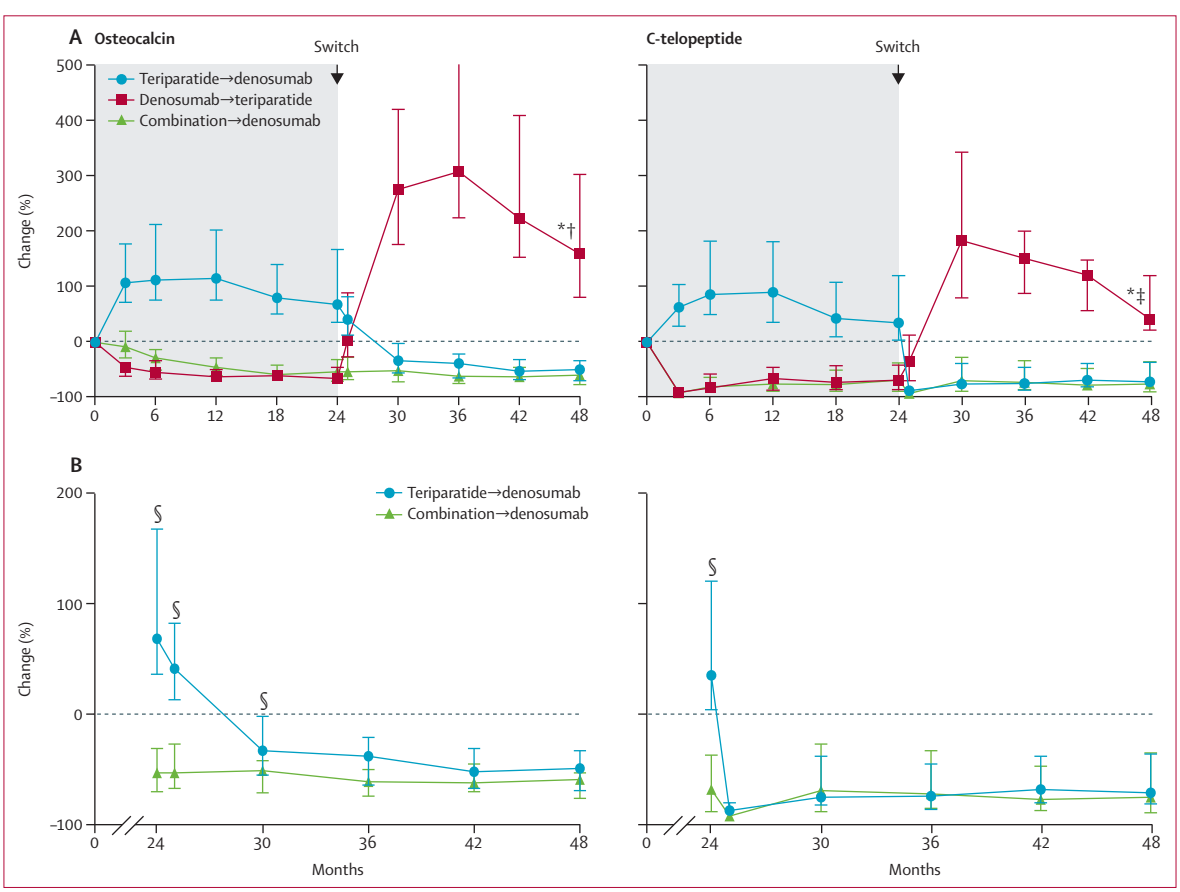

Figure 4: **Median percent change (IQR; error bars) in osteocalcin and C-telopeptide from baseline to 48 months (A) and baseline to 24–48 months in the teriparatide to denosumab group and combination to denosumab group (B)**

*p<0·0001 versus combination to denosumab at months 24, 25, 30, 36, 42, and 48. †p<0·0001 versus teriparatide to denosumab at months 24, 30, 36, 42, and 48; p=0·41 at month 25. ‡p<0·0001 versus teriparatide to denosumab at months 25, 30, 36, 42, and 48; p=0·36 at month 24. §p<0·05 compared with combination to denosumab at the indicated timepoints.

(5·6% [SD 4·5]) were larger than in either the combination to denosumab group (2·1% [4·9]; p=0·0156) or the denosumab to teriparatide group (1·2% [4·9]; p=0·0019).

After 24 months of the originally assigned therapy, mean bone mineral density at the distal radius had increased in the denosumab and combination groups, whereas it decreased in the teriparatide group.[8] When patients originally treated with denosumab switched to teriparatide, radius bone mineral density progressively decreased resulting in net 0–48-month decrease of –1·8% (SD 5·9). At the conclusion of DATA-Switch, radius shaft bone mineral density had increased by 2·8% (SD 3·2) in the combination to denosumab group and reverted to the original baseline in the teriparatide to denosumab group (0·0% [2·9]). The 0–48-month bone mineral density increases at the distal 1/3 radius in the combination to denosumab group were significantly larger than those either in the teriparatide to denosumab group (p=0·0075) or the denosumab to teriparatide group (p=0·0099).

In women treated with denosumab followed by teriparatide, median osteocalcin increased by 275% (IQR 176–410) above the original baseline after 6 months of teriparatide (month 30) and remained 159% (81–302) over the original baseline even after 24 months of teriparatide (month 48; figure 4A, B). In these same women, C-telopeptide concentrations increased by 183% (IQR 80–343) at month 30 and were 42% (22–120) above baseline at month 48. In women treated with teriparatide followed by denosumab, the changes in bone resorption and formation showed different patterns. Bone resorption (C-telopeptide) was maximally suppressed after 1 month of denosumab, whereas bone formation (osteocalcin) was not maximally suppressed until 12–24 months of denosumab treatment. In women treated with combination therapy followed by denosumab monotherapy, however, both markers were maximally suppressed at all post-switch timepoints. When comparing women in the teriparatide to denosumab group with women in the combination to denosumab group (both of which are receiving the same treatment from month 24–48), serum osteocalcin was significantly higher in those switching from teriparatide monotherapy to denosumab monotherapy than in those switching from combination therapy to denosumab monotherapy at 1 months and 6 months after the transition (months 25 and 30; p<0·0001 at month 25 and p<0·0023 at month 30). Conversely, C-telopeptide in these two groups did not differ at any timepoint after the treatment transitions.

Significant hypercalcaemia (blood calcium >10·8 mg/dL confirmed on repeat testing) was identified in one patient during months 24–48 (denosumab to teriparatide group). Serious adverse events were reported in six participants in the teriparatide to denosumab group (ductal carcinoma in situ of the breast, syncope, chronic obstructive pulmonary disease exacerbation, elective cervical laminectomy, fundoplication procedure, and non-ST elevation myocardial infarction), four participants in the denosumab to teriparatide group (appendicitis, laryngitis or pharyngitis, nephrolithiasis without hypercalcaemia, and anaemia due to a gastric ulcer), and three participants in the combination to denosumab group (breast cancer, atrial fibrillation, and atrial fibrillation with stroke). With the exception of the patient with nephrolithiasis, which was classified as possibly related to treatment (teriparatide), the other serious adverse events were classified as unrelated to therapy by the study investigators and an independent safety monitoring board.

Discussion

In this study, we have shown that in postmenopausal osteoporosis, switching therapy from teriparatide to denosumab further increases bone mineral density at all measured sites, whereas switching therapy from denosumab to teriparatide results in transient bone loss at the hip and spine and progressive bone loss at the radius shaft. Additionally, we have shown that 24 months of combined therapy followed by 24 months of denosumab alone is associated with largest cumulative bone mineral density increases at the hip and radius, increases that are greater than have been reported with any currently available therapy taken for a similar duration.[14–17]

These findings have several important clinical ramifications. First, this study shows the importance of the order of anabolic versus antiresorptive therapy with denosumab. The bone loss that occurs in patients switching from denosumab to teriparatide was an unexpected finding. Studies investigating the effects of teriparatide after bisphosphonates report further increases in bone mineral density, although generally smaller increases than those observed when teriparatide is given to a patient who has not received previous bisphosphonate therapy.[18–23] It was postulated that because bisphosphonates are present in the bone matrix for years after administration,[24] teriparatide-induced increases in bone turnover were being inhibited in a manner similar to that noted when bisphosphonates are given concurrently with teriparatide or parathyroid hormone.[10–12] If this hypothesis had been correct, one might have expected that the administration of teriparatide after denosumab would not be associated with this blunting and would allow for the full anabolic effect of teriparatide to proceed. Indeed, our data do show that there is no blunting of teriparatide-induced stimulation of bone turnover after denosumab therapy. By contrast, bone resorption and formation increased more after switching from denosumab to teriparatide than when the DATA patients were treated with teriparatide de novo. Bone resorption, as measured by median C-telopeptide, increased by 183% during the original baseline 6 months after switching from denosumab to teriparatide and bone formation, as measured by median osteocalcin, increased by 275%. Notably, this degree of stimulation of bone metabolism is much greater than in the same women

treated with teriparatide de novo, who in the DATA study had a 6-month median C-telopeptide increase of 86% and a 6-month median osteocalcin increase of 112% (figure 4B). It is also significantly greater than the magnitude of the reported so-called overshoot in bone turnover noted in patients stopping denosumab after 24 months of treatment.[7]

The mechanism by which teriparatide exerts such a large effect on bone metabolism in patients discontinuing denosumab is unknown, but could relate to teriparatide stimulating a large pool of dormant osteoclast precursors in patients in whom RANKL inhibition has been sustained for 2 years.

The substantial increase in bone mineral density in women switching from teriparatide to denosumab is consistent with studies reporting that bisphosphonates further increase bone mineral density when given after parathyroid hormone or teriparatide.[25,26] In this study, it should be noted that the increases in bone mineral density in women treated with teriparatide monotherapy followed by denosumab were even greater than in those treated with combination teriparatide plus denosumab therapy followed by denosumab alone. The mechanism underlying the greater 24–48-month increases in the teriparatide to denosumab group could relate to the changed relation between bone formation and bone resorption in these patients. Specifically, bone resorption, as measured by C-telopeptide, is more quickly suppressed after transitioning from teriparatide to denosumab than is bone formation, as measured by osteocalcin. This discrepancy probably allows for a several month period of relative unlinking of bone formation and resorption, which favours the accrual of bone mass. It is, notably, a very similar unlinking that we hypothesised mechanistically explains the larger increases in bone mineral density achieved by combination teriparatide–denosumab therapy in the initial 12 months of osteoporosis treatment.[9] It is also notable that despite the so-called catch up in bone mineral density gains achieved in women transitioning from teriparatide to denosumab, women treated initially with combined therapy followed by denosumab had the most favourable 48-month bone mineral density changes at the total hip and distal radius, the two measured sites with the highest proportion of cortical bone. In view of the importance of cortical bone mass in maintaining skeletal integrity, the noted persistent benefit at these anatomic sites would be expected to confer significantly greater bone strength to these patients.[27,28] Moreover, although studies undertaken in different populations cannot be precisely compared, it is notable that the total bone mineral density increases achieved in both the combination to denosumab and teriparatide to denosumab groups are larger than those noted with any one drug given for a similar period of treatment. Specifically, the reported 4-year bone mineral density gains with either denosumab or zoledronic acid are less than 12% at the spine and less than 6% at the femoral neck.[16,17]

Our study has several limitations. First, the size of the study precludes an assessment of the relative safety or antifracture efficacy of the three assigned treatment regimens. Bone mineral density, however, has proven to be a reliable, although imperfect, predictor of antifracture efficacy in patients treated with osteoporosis drugs, including denosumab and teriparatide.[29,30] Additionally, the specific clinical impact of the transient bone loss that occurs in women switching from denosumab to teriparatide cannot be precisely estimated. It is notable, however, that several studies have reported that both elevated markers of bone turnover and increased rates of bone loss are associated with increased fracture risk.[31–35] Consistent with these studies, it has also been reported that postmenopausal women who discontinue oestrogen (and hence have increased bone turnover) have an increased risk of hip fracture than do women who never used oestrogen.[36] Thus, even without specific fracture data, we feel that the practising physician must consider these factors before recommending drug changes or initiating therapy in their osteoporotic patients.

The open-label design is a potential limitation. The potential for bias is limited, however, in that the physicians interpreting the dual x-ray absorptiometry measurements and the laboratory who did the bone marker assays were masked to treatment assignment. Additionally, the women who entered the DATA-Switch were only a subset of those originally randomised in the parent DATA study. That said, our retention in this 24-month extension of a 24-month randomised controlled trial is quite strong and no significant differences were noted in any demographic or clinical parameter between those participants who participated in DATA-Switch and the original DATA cohort. Finally, our study population is at somewhat lower risk of fracture than those for whom this type of intensive therapy might be recommended and thus should be considered as a proof-of-concept study, supporting a more definitive trial with a fracture-reduction endpoint.

In postmenopausal osteoporosis, the order in which denosumab and teriparatide are used has a significant effect on overall treatment effectiveness. Specifically, teriparatide does not adequately prevent bone loss after denosumab, whereas denosumab stabilises and further increases bone mineral density when used after teriparatide or combination therapy. Furthermore, the largest increases in bone mineral density at the hip and wrist, and the largest bone mineral density increases possible in any clinical context, are achieved in women treated with 24 months of combined teriparatide plus denosumab followed by 24 months of denosumab monotherapy. These results should influence the approach to the initial and sequential treatment of osteoporotic women, particularly those with established disease who are at an acutely high risk of fragility fracture.

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Contributors
BZL, JNT, AVU, S-AMB-B, RMN, and HL conceived and designed the study. BZL, JNT, AVU, S-AMB-B, HL, and PMW collected, analysed, and interpreted the data. BZL, JNT, and PMW drafted the report. BZL, JNT, AVU, S-AMB-B, RMN, HL, and PMW critically revised the report for important intellectual content. HL did the statistical analysis. BZL obtained the funding.

Declaration of interests
BZL serves as a consultant for Eli Lilly, Amgen, Merck, and Radius Health and receives research support from Lilly and Amgen. RMN is a consultant to Eli Lilly and Radius Health Inc. All other authors declare no competing interests.

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