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Context: Teriparatide and denosumab are effective treatments for osteoporosis and typically reserved as second-line options after patients have used bisphosphonates. However, limited head-to-head comparative effectiveness data exist between teriparatide and denosumab.
Objective: We compared changes in bone mineral density (BMD) between groups treated with teriparatide or denosumab after using bisphosphonates, focusing on the change in BMD while on either drug over 2 years.
Design: Observational cohort study using electronic medical records from two academic medical centers in the US.
Participants: The study population included osteoporotic patients > 45 years who received bisphosphonates over one year prior to switching to teriparatide or denosumab.
Outcome Measures: Annualized BMD change from baseline at the lumbar spine, total hip and femoral neck.
Results: Patients treated with teriparatide (n=110) were compared to those treated with denosumab (n=105); the mean (SD) age was 70 (10) years and median duration (IQR) of

bisphosphonate use was 7.0 (5.6-9.7) years. Compared to denosumab users, teriparatide users had higher annualized BMD change at the spine by 1.3% (95% CI 0.02, 2.7%), but lower at the total hip by -2.2% (95% CI -2.9 to -1.5%) and the femoral neck by -1.1% (95% CI -2.1 to -0.1%). Those who switched to teriparatide had a transient loss of hip BMD for the first year, with no overall increase in the total hip BMD over two years.

Conclusions: Among patients who use long-term bisphosphonates, the decision of switching to teriparatide should be made with caution, especially for patients at high risk of hip fracture.

This is a head-to-head comparison study using 14 years electronic medical records. We compared teriparatide versus denosumab on BMD in patients switching from long-term bisphosphonate.

INTRODUCTION

Therapeutic options for osteoporosis have increased over the past two decades (1). Bisphosphonates are the most widely used anti-osteoporosis agents in clinical practice (2–4). The anabolic agent teriparatide (human parathyroid hormone 1-34) and the antiresorptive agent denosumab (monoclonal antibody to receptor activator of nuclear factor kappa-B ligand) are potent drugs often reserved as second-line treatments for patients who lose bone mineral density (BMD) or fracture while on a bisphosphonate, or who have severe disease(1).

In randomized controlled trials (RCT) of bisphosphonate-naïve patients, the estimated fracture risk reduction using denosumab was 68% for vertebral fractures and up to 20% for nonvertebral fractures at 12 months, compared with placebo (5). In similar trials, teriparatide reduced vertebral fractures by 65% and nonvertebral fractures by 63% compared with placebo over a median follow-up of 21 months(6). However, there is some evidence that prior anti-resorptive therapy – in particular bisphosphonates – may influence the effects of both teriparatide(7–12) and denosumab(13). Over 63% of teriparatide users(14) and 54% of denosumab(15) users in the US had been prescribed a prior anti-osteoporosis agent, mostly bisphosphonates. Thus, the therapeutic effect of teriparatide and denosumab in typical clinical practice may not be the same as reported in clinical trials.

There is only one head-to-head RCT comparing denosumab and teriparatide that included participants who switched from long-term bisphosphonates, but almost two-thirds of patients in this trial were bisphosphonate-naïve(16). This head-to-head trial showed that denosumab and teriparatide improved BMD similarly at the lumbar spine, total hip and femoral neck over 24 months. An indirect meta-analysis that included mostly bisphosphonate-naïve patients showed that teriparatide increased BMD 2.6% more than denosumab at the spine, but 1.3% less than denosumab at the total hip over 24 months(17). These data conflict regarding the optimal medication if further treatment is needed after bisphosphonate use.

We used real-world data to compare the effectiveness of switching to teriparatide versus denosumab on BMD in patients with prior long-term bisphosphonate-use.

METHODS

Study design

In a group of patients who had used bisphosphonates for over 12 months, we compared changes in BMD between those switching to teriparatide or denosumab. The primary outcomes were the differences in annualized BMD change from baseline between two agents at the lumbar spine, total hip and femoral neck for 2 years.

Study population and data sources

Partners HeathCare electronic medical record (EMR) is used by several hospitals, including Brigham and Women's Hospital and Massachusetts General Hospital. These hospitals provide care for approximately 4.6 million patients in and around Boston, Massachusetts. We used the medical records of patients who took osteoporosis medications from Jan 2004 to Dec 2017.

Potentially eligible patients were over 45 years of age and had used at least 12 months of prior bisphosphonate, including alendronate, ibandronate, risedronate, pamidronate or zoledronic acid. They were required to have subsequently used teriparatide or denosumab for more than 6 months, and undergone at least two dual-energy X-ray absorptiometry (DXA) scans as detailed below. From this group of potentially eligible patients, the following exclusion criteria were applied: a history of Paget's disease, simultaneous use of denosumab, teriparatide and/or bisphosphonates, high-dosage denosumab (120 mg/ month) (prescribed for cancer patients), and a prior course of teriparatide. The Partners HealthCare Institutional Review Board approved all aspects of this study.

Exposure and outcome assessment

The exposure of interest was treatment with teriparatide or denosumab after at least 12 months of bisphosphonate use. First, we identified all patients who had a least one prescription of teriparatide or denosumab through an automated search of the EMR, then drug usage details (duration and dosage) were verified by one author (HL) through chart review. For each patient, the dose, duration and reason for discontinuation were documented based on the chart review. The date of the first dose of denosumab or teriparatide was defined as the index date. We classified drug brand or generic names into four categories: oral bisphosphonates (alendronate 10 mg once daily or 70 mg once weekly, ibandronate 150 mg once monthly, risedronate 35 mg once weekly, 75 mg on two consecutive days every months or 150 mg once monthly), intravenous bisphosphonate (zoledronic acid 5 mg once yearly or 2.5 mg every 6 months, ibandronate 3 mg every 3 months, pamidronate 60 mg every 6 months or 30 mg every 3 months), denosumab (60 mg subcutaneous every 6 months) and teriparatide (20 μg subcutaneous daily) for each patient.

We extracted BMD (g/cm^2) from routine DXA scans (QDR 4500/4500A; Hologic, Bedford, MA) of the posteroanterior lumbar spine, total hip, and femoral neck. The baseline DXA test window was defined as 2 years before through 3 months after the index date. Follow-up of teriparatide and denosumab use was truncated at 27 months to achieve similar drug exposure durations for both treatment groups. Thus, the follow-up DXA test window was defined as 6 to 27 months after the index date so as to include all qualified DXA tests in this window. For patients with multiple DXA tests within the baseline or follow-up window, the DXA closest to the index date or last date of drug use were chosen. All interim DXA tests between baseline and last DXA were included for analysis(18).

Covariate assessment

Patient characteristics were collected from the EMR. Variables of interest included age, sex, race, body mass index (BMI), other medications related to bone mineral density (hormone replacement therapy, raloxifene, glucocorticoids) and comorbidities included in the Charlson comorbidity index(19). Comorbidities were defined using corresponding International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or ICD-10-CM codes before the index date. We also collected information on prior fragility fractures(20) defined as those occurring in the year prior to the index date. Prior bisphosphonate treatment (duration and washout period) was verified by chart review. Duration of prior bisphosphonate use was defined as the combined duration of all bisphosphonates (alendronate, ibandronate,

risedronate, pamidronate or zoledronic acid). The washout period was defined as the interval between bisphosphonate cessation and initiation of denosumab or teriparatide.

Statistical analyses

Baseline characteristics were compared between the two groups using descriptive statistics. There were imbalances between the two groups in baseline characteristics, thus we used matching weights - an extension of inverse probability of treatment weighting method - to improve balance across the two treatment groups(21,22). We first fit a propensity score logistic model in which the treatment group (teriparatide or denosumab) was the dependent variable and all potential confounders (age, sex, race, BMI, prior oral bisphosphonate duration, prior intravenous bisphosphonate duration, prior bisphosphonate washout period, baseline BMD, prior fragility fracture, glucocorticoids history, HRT history, raloxifene history, hyperthyroidism, any malignancy, renal disease, rheumatoid arthritis, osteoarthritis, esophageal disease, diabetes, anemia, hypertension, hyperlipidemia, congestive heart disease, peripheral cardiovascular disease, stroke, COPD, hemiplegia or paraplegia and Charlson comorbidity index) were independent variables. The predicted probability from this model represents each patient's probability of receiving teriparatide. These probabilities were used to assign each patient a weight, such that the weighted teriparatide group and weighted denosumab group were balanced in their baseline characteristics(23), similar to a 1:1 propensity score-matched cohort. In contrast to propensity score matching, the weighting method retains all patients, thereby maximizing the use of all available data(21,22).

We then used weighted generalized estimating equations (GEE) to compare BMD change in the treatment groups. Change in BMD from baseline to follow-up was modeled as a linear term to provide annualized change estimates. The models included interaction terms between the treatment group and the time variable; their coefficients are interpreted as the difference in annualized change between the two treatments. To aid interpretability and comparability with prior clinical trials(5,6,24–26), we calculated the percentage change in BMD from baseline. To explore non-linear BMD changes, we performed the same analysis with time categorized into baseline (-24 to 3 months), 12 months (9 to 15 months) and 24 months (21 to 27 months). Since consolidation with anti-resorptive agents are typically recommended after 2 years of teriparatide, we also estimated BMD response through the consolidation stage, thus assessing denosumab over 4 years and teriparatide for 2 years plus 2 further years of consolidation.

We performed a series of sensitivity analyses to test the robustness of the primary analysis. First, we conducted a 1:1 propensity score-matched analysis using greedy matching within a caliper of 0.1 standard deviations of the propensity score to provide estimates for a subgroup matched for baseline characteristics. Second, since percentage change from baseline might be vulnerable to extreme values, we repeated the same analysis with actual BMD (g/cm^2) and converted resulting differences to percentage change from the mean baseline BMD (27). Third, we repeated the above analyses excluding patients who had baseline DXA >12 months before the index date to improve the accuracy of baseline BMD. Fourth, we excluded patients with very low BMD (the lowest 10%) to further improve comparability between the two groups. Fifth, patients who did not complete two years of treatment were excluded. Sixth, patients in the teriparatide group with index date before June 6, 2010 were excluded, as denosumab was not on the market before this date. Last, we excluded rare cases of patients who had >10 years of prior bisphosphonate use. All analyses were performed using R-3.4.3 (https://cran.r-project.org).

RESULTS

Among 778 patients with at least one prescription of denosumab or teriparatide, 215 patients were eligible for the current analysis (**Figure 1**). Patients were 94% female with a mean (SD) age of 70 (10) years. The median duration (interquartile range [IQR]) of prior bisphosphonate use was 7.0 (5.6-9.7) years.

The baseline characteristics of the two exposure groups are shown in **Table 1**. Most baseline characteristics were quite similar between the two groups. The teriparatide group had lower BMD at all three anatomic sites (the lumbar spine, total hip and femoral neck), shorter duration of prior bisphosphonate and lower prevalence of prior fractures than denosumab group. After applying propensity score-based weighting, baseline characteristics were well balanced across both exposure groups(28). Potential confounders such as age, BMI, hyperthyroidism, esophageal disease, prior fragility fracture, any malignancy, hemiplegia/paraplegia, rheumatoid arthritis, osteoarthritis, baseline BMD (the lumbar spine, total hip, and femoral neck) and prior bisphosphonate treatment duration, were all balanced between the two exposure groups (**Table 1**). In the 1:1 propensity score-matched subset, the above mentioned potential confounders were also adequately balanced(29).

Differences in BMD change between teriparatide and denosumab

In the weighted analyses, denosumab significantly increased BMD at all three anatomic sites (the lumbar spine, total hip and femoral neck), while teriparatide only significantly increased BMD at the lumbar spine (**Table 2**). Over 2 years, compared to denosumab, teriparatide users had greater annualized BMD increase at the spine by 1.3% (95% CI 0.02 to 2.7%, p=0.046), but also greater annualized BMD loss at the total hip by -2.2% (95% CI -2.9 to -1.5%, p <0.001) and femoral neck by -1.1% (95% CI -2.1 to -0.1%, p=0.029).

Non-linear BMD change trajectories for teriparatide and denosumab are shown in **Figure 2**. Teriparatide and denosumab demonstrated different changes in BMD; patients who switched to teriparatide showed a non-significant trend for greater increases in lumbar spine BMD than denosumab through the first 2 years. However, teriparatide users had BMD loss at the hip (both total hip and femoral neck) in the first year, with no overall change over 2 years. During the consolidation stage, teriparatide users had continued BMD response at lumbar spine through 36 and 48 months, but responses at the hip areas were lower compared to values observed at the lumbar spine(30).

Sensitivity analyses

Effect size estimates from sensitivity analyses were consistent with the primary analysis (**Figure 3**). Since most sensitivity analyses only included a subset of the original study population, especially for the 1:1 propensity score-matched analysis, they were less efficient and had wider confidence intervals than the primary analysis. For lumbar spine BMD, differences between the two treatments ranged from 0.7 to 2.4%. For the total hip, teriparatide had lower annualized BMD increase than denosumab, with estimated differences ranging from -1.7 to -2.7%. At the femoral neck, teriparatide again had lower annualized BMD increases than denosumab, with the estimated difference ranging from -0.2 to -1.4%.

DISCUSSION

In this observational study of long-term bisphosphonates users, annualized BMD increase after switching to teriparatide was 1.3% higher at the lumbar spine, and lower by 2.2% at the total hip and 1.1% at the femoral neck, compared to switching to denosumab. Those who switched to teriparatide had a transient loss of hip BMD for the first year, with no overall increase in total hip

BMD over two years. In patients with long-term bisphosphonate-use, our results suggest that clinical decisions to switch to teriparatide should be made with caution, especially for patients at high risk of hip fracture.

In our study, the 2.2% annual difference in total hip BMD between teriparatide and denosumab groups and 1.1% at the femoral neck may suggest a clinically meaningful difference in fracture risk reduction. BMD change is regarded as the most important surrogate for evaluating therapeutic response. A recent meta-analysis of 21 randomized trials showed that changes in hip BMD over two years explained 60-65% of the treatment-related reduction in fracture risk(31), although only some of the data are from patients with prior bisphosphonates use. More specifically, a 3% increase in hip BMD at 1 year was associated with a 46% reduction in nonvertebral fracture risk(32).

The efficacy of teriparatide and denosumab are different between bisphosphonate-naïve patients and long-term bisphosphonates users. Previous results of randomized clinical trials found that teriparatide increased total hip BMD by 2.6%(6) and denosumab 3.6% at 12 months in treatment-naïve patients(26). However, in long-term bisphosphonate treated patients, the effect sizes were much smaller, total hip BMD increase at 12 months after switching to teriparatide was -0.9% and denosumab 2.0% (**Figure 2**).

The hip BMD response using teriparatide in prior bisphosphonates users was less than expected. There are possible mechanistic reasons for these findings. With long-term bisphosphonate-use, bone turnover is inhibited, and cortical bone is highly mineralized. At cortical sites such as the hip, teriparatide induces absorption of old bone matrix and apposition of new bone matrix, not yet fully mineralized(8,33,34). A transient fall in BMD can be seen at the beginning of teriparatide therapy due to the resorption of highly mineralized old bone and subsequently increased cortical porosity (8,35,36). BMD then slowly increases with ongoing treatment as new bone fully mineralizes. In our patients who had a median duration of prior bisphosphonate-use of 7 years, BMD gained by new bone mineralization may be offset by old bone resorption for at least the first year. In contrast, denosumab binds and inhibits receptor activator of nuclear factor-κB ligand to achieve extensive suppression of bone turnover and increases BMD at all skeletal sites(37). Switching to denosumab increases BMD even after long-term anti-resorptive therapy (38). Transition to denosumab from alendronate produced greater in BMD at all measured anatomic sites and a further reduction in biochemical markers of bone turnover(38).

The poor hip BMD response in patients switching from bisphosphonates to teriparatide highlights the importance of drug sequence when using anabolic and anti-resorptive agents(7,9,16,39–41). Cosman et al. summarized BMD changes at the hip in various published clinical trials investigating the effects of teriparatide when used after an antiresorptive agent(7). BMD at the hip fell below baseline values for the first 12 months after switching, resulting a decrease of -2.7 to -0.3% in total hip BMD, but returned to baseline at 18 months (-1.7 to 0.9%) and almost increased above baseline by 24 months (-0.7 to 2.9%)(8–10,42,43). Our study showed similar BMD trajectories: hip BMD dropped for the first 12 months and then returned to the baseline level. Since switching to teriparatide in prior bisphosphonate-treated patients does not achieve optimal BMD gain at all sites, and teriparatide can only be used for 24 months, this routinely used strategy needs examination.

To maximize the treatment effect, substantial data suggest using teriparatide before bisphosphonates (44–46). In one study, teriparatide followed by bisphosphonates had better BMD gains than bisphosphonates followed by teriparatide(47). Over a period of 19 to 24

months, teriparatide achieved an average gain of approximately 3% in the hip area (total hip and femoral neck). After teriparatide, the transition to a bisphosphonate led to 2% additional increase in the hip area after 1 year(46). We evaluated prescription patterns in our study population and observed that teriparatide followed by bisphosphonates was rarely used. The most widely used pattern in the last decade at Partners HealthCare was bisphosphonates followed by teriparatide. We examined the BMD increase profile of this pattern and did not identify a relative gain in BMD during the 2-year treatment compared with teriparatide followed with anti-resorptive agents in a prior study(46). Thus, in patients who are likely to require more than one drug, previous sequential studies(8–10,42,46,48) and our results suggest initial use of teriparatide followed by an antiresorptive as an alternative choice to achieve maximal gains in BMD(41).

The main strength of this study is that we used 14 years of observational data to emulate a randomized trial comparing the effectiveness of denosumab vs. teriparatide when an RCT is not available. While theoretically possible, it is unlikely that an RCT will ever be conducted for this question. Thus, results of the current study provide an important piece of information for clinical decision-making. This study not only showed a transient decrease for teriparatide in the hip areas but also provided a contrast with denosumab, suggesting switching to teriparatide should be made with caution, especially for patients at high risk of hip fracture. We applied several rigorous methods to reduce bias and confounding in both study design and data analysis. First, we used an active-comparator and new-user design to help mitigate confounding by design and facilitate confounding adjustment by establishing correct temporality between pretreatment variables and drug exposure(49,50). Second, we balanced the baseline characteristics between two groups using matching weights, an extension of inverse probability of treatment weighting method, and estimated BMD increase with marginal structural models.

Despite these rigorous methods, our study still has limitations. First, unlike a randomized controlled trial, which can balance both the measured and unmeasured confounders, head-to-head comparison with observational data can only balance the measured confounders using statistical approaches, there is possibility for unmeasured confounding that could create bias. For example, concomitant use of proton pump inhibitors would reduce BMD; if patients who switched to teriparatide were more likely to use proton pump inhibitors, then this would be an unmeasured confounder. However, compared to the effect of bisphosphonate, glucocorticoids and HRT, the effect of such proton pump inhibitors might be minor. Second, this was a retrospective study using routine clinical data; therefore not all patients in the source population underwent sufficient numbers of DXA tests to describe BMD changes, leading to the exclusion of over half study population during the selection process. Current guidelines(1,51) recommend the same DXA monitoring schedule (1 or 2 years after initiating osteoporosis drugs) for patients who switched to denosumab or teriparatide. Thus the risk of selection bias is low. Sensitivity analysis using patients who had baseline DXA >12 months before switching produced similar results. Third, our primary analysis assumed that patients who switched to denosumab or teriparatide were from the same population, despite teriparatide (2001) and denosumab (2010) having different marketing dates. An additional sensitivity analysis restricted to switching after June 2010 reached the same conclusions. Fourth, the various bisphosphonates used in the period before switching to teriparatide or denosumab have an inherent difference in efficacy, and our study did not have enough power to study the interaction between response and prior bisphosphonate type. Last, we did not evaluate the difference in fracture events due to low fracture incidence in the study cohorts. As the evidence on BMD change and fracture risk reduction are based on data using anti-resorptive agents, further studies using fracture endpoints

are needed to confirm the efficacy difference between teriparatide and denosumab in patients treated with prior bisphosphonates.

CONCLUSION

Among long-term bisphosphonate users that switched to a different class of osteoporosis treatment, denosumab and teriparatide both increased BMD at the spine, but BMD increases at the total hip and femoral neck were greater in the denosumab group. Switching to teriparatide led to a transient BMD loss at the hip for the first year, but whether this loss affects fracture risk is unknown. In this particular population, our results suggest the decision of switching to teriparatide should be made with caution, especially for patients at high risk of hip fracture. Future trials or large observational studies comparing fracture end-points with special focus on the first 2 years after switching are needed to support our findings.

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DISCLOSURE SUMMARY

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Data Availability

Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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Figure 1. Flow chart showing the cohort selection process.

Figure 2 BMD change trajectories of switching to denosumab versus teriparatide in patients with prior bisphosphonate-use. Teriparatide and denosumab demonstrated different changes in BMD; patients who switched to teriparatide showed a non-significant trend for greater increases in lumbar spine BMD than denosumab through the first 2 years. However, teriparatide users had BMD loss at the hip (both total hip and femoral neck) in the first year, with no overall change over 2 years. Time categorized into baseline (-24 to 3 months), 12 months (9 to 15 months) and 24 months (21 to 27 months).

Figure 3 Sensitivity analyses for the BMD increase differences between denosumab and teriparatide. Effect size estimates from sensitivity analyses were consistent with the primary analysis at all the three sites (the lumbar spine, total hip, and femoral neck).

Table 1 Baseline characteristics of study cohorts before and after weighting

Variables	Unweighted cohort			Weighted cohort		
	DMAb	TPTD	SMD	DMAb	TPTD	SMD
N	105	110		-	-	

Age (mean)	70.2	70.3	0.014	67.9	66.8	0.018
Male (%)	7.6	4.5	0.129	5.4	5.8	0.015
Race (White, %)	93.3	91.8	0.058	90.2	90.3	0.003
BMI (mean)	24.1	22.8	0.287	23.2	23.9	0.049
Smoking history (%)	23.8	10.9	0.346	12.2	12.0	0.010
Obesity (%)	18.1	8.2	0.297	9.6	11.9	0.082
Hyperthyroidism (%)	12.4	12.7	0.010	13.1	13.8	0.020
Esophagus disease (%)	54.3	41.8	0.252	42.3	42.2	0.002
Any malignancy (%)	36.2	11.8	0.595	16.8	17.0	0.005
Renal disease (%)	29.5	9.1	0.536	10.6	11.4	0.024
Diabetes (%)	24.8	14.5	0.259	17.0	16.6	0.012
Hypertension (%)	64.8	57.3	0.154	57.6	57.0	0.012
Hyperlipidemia (%)	78.1	69.1	0.205	70.8	72.4	0.034
Cerebrovascular disease (%)	18.1	19.1	0.026	11.3	9.7	0.053
Chronic pulmonary disease (%)	36.2	37.3	0.022	37.7	38.0	0.006
Anemia (%)	48.6	37.3	0.230	43.9	45.3	0.028
Hemiplegia or paraplegia (%)	21.9	14.5	0.192	13.7	14.2	0.015
Rheumatoid arthritis (%)	11.4	13.6	0.067	5.9	5.5	0.014
Osteoarthritis (%)	65.7	59.1	0.137	59.2	57.4	0.036
Charlson comorbidity index (mean)	3.8	2.1	0.554	2.4	2.6	0.013
Fractures						
Fragility fracture (%)	36.2	50.9	0.300	39.4	36.3	0.063
BMD						
Lumbar spine (T-score)	-2.3	-2.7	0.396	-2.4	-2.3	0.061
Total hip (T-score)	-1.9	-2.3	0.467	-2.0	-1.9	0.046
Femoral neck (T-score)	-2.3	-2.5	0.372	-2.3	-2.2	0.057
Lumbar spine (g/cm2)	0.79	0.74	0.402	0.77	0.78	0.059
Total hip (g/cm2)	0.71	0.66	0.474	0.70	0.71	0.042
Femoral neck (g/cm2)	0.60	0.57	0.384	0.60	0.61	0.054
Osteoporosis agents						
Prior oral BP duration (years)	5.9	6.8	0.199	6.6	6.7	0.008
Prior intravenous BP duration (years)	1.4	0.8	0.271	1.1	1.2	0.045
Glucocorticoids (%)	60.0	55.5	0.092	57.0	54.0	0.067
HRT (%)	36.2	46.4	0.208	44.7	41.9	0.057
Raloxifene (%)	9.5	13.6	0.129	11.9	11.3	0.016
BP washout period (month)	24.4	9.7	0.607	14.6	15.7	0.043

DMAb, denosumab; TPTD, teriparatide; SMD, standardized mean difference; BMI, body mass index; BMD, bone mineral density; BP, bisphosphonates; HRT, hormone replacement therapy;

Table 2 Difference in annualized percentage BMD change between denosumab and teriparatide over 2 years

Site	Therapy	Mean annualized BMD changes from baseline % (95% CI)	Difference between teriparatide and denosumab % (95% CI)	P value
Lumbar spine	Denosumab	3.1 (2.3, 3.9)	Reference	
	Teriparatide	4.4 (3.4, 5.5)	1.3 (0.02, 2.7)	0.046
Total Hip	Denosumab	1.9 (1.5, 2.4)	Reference	
	Teriparatide	-0.3 (-0.8, 0.3)	-2.2 (-2.9, -1.5)	<0.001
Femoral neck	Denosumab	1.8 (1.2, 2.4)	Reference	
	Teriparatide	0.7 (-0.2, 1.5)	-1.1 (-2.1, -0.1)	0.029

Weighted generalized estimating equations (GEE) were used to compare BMD change in the weighted cohorts. Change in BMD from baseline to follow-up was modeled as a linear term to provide annualized change estimate.