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ORIGINAL ARTICLE

The impact of teriparatide adherence and persistence on fracture outcomes

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Abstract
Summary The study investigated the real-world relationship between teriparatide adherence and persistence and fracture outcomes in a US claims database. Fracture risk was estimated to decrease as adherence and persistence increased for any clinical, vertebral, and non-vertebral fractures. Greater emphasis on programs to increase patient adherence may improve clinical outcomes.
Introduction Adherence to osteoporosis treatment is essential for achieving optimal therapeutic outcomes. Previous findings from clinical trials and observational studies demonstrate that longer teriparatide (TPTD) exposure is associated with fewer fractures. The study aim was to investigate real-world relationships between TPTD adherence and persistence and fracture outcomes.
Methods The Thomson Reuters MarketScan® database, 2004–2008, was used to identify TPTD users with continuous enrollment 12 months pre- and 24 months post-TPTD initiation. Post-index fractures included vertebral and non-vertebral. Adherence (medication possession ratio, MPR) groups were defined as high (MPR≥0.80), medium (0.5≤MPR<0.8), and low (MPR<0.5). Persistence groups were defined by periods 1–6, 7–12, 13–18, and 19–24 months. Logistic regressions modeled fracture risk for any clinical, hip, vertebral, and non-vertebral fractures, controlling for patient characteristics, insurance and healthcare provider types, Charlson comorbidity index, bone mineral density screening, medication use, and fracture history.
Results Among 3,587 TPTD patients (mean age 68.9 years; 91% female), fracture risk was lowest in high MPR patients in all models except hip (OR=1.17; p=0.64). Medium versus high MPR was a significant risk factor for any fracture (OR=1.49; p=0.004) and non-vertebral fracture (OR=1.45; p=0.014); low-MPR was a significant risk factor for any fracture (OR=1.64; p<0.01), vertebral fracture (OR=2.56; p=0.001), and non-vertebral fracture (OR=1.44; p=0.013). Persistence of 1–6 months versus 19–24 months was associated with higher risk for any clinical (OR=1.88, p<0.001), vertebral (OR=3.69; p<0.001), and non-vertebral fracture (OR=1.51; p=0.011), but not hip (OR=1.93; p=0.08).
Conclusions Fracture risk decreased as TPTD adherence and persistence increased for any clinical, vertebral, and non-vertebral fractures.

Keywords Adherence · Fractures · Osteoporosis · Outcomes · Persistence · Teriparatide

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Introduction

Osteoporosis is the most common chronic bone disease affecting approximately 10 million people over age 50 in the USA [1]. Another 18 million individuals have low bone mass and are at increased risk of the disease and its potential complications [2]. Total fractures and costs from osteoporosis in 2010 in the USA are estimated at over

2.2 million and $18.7 billion [3]. Available treatments for osteoporosis include anti-resorptive agents [bisphosphonates, a selective-estrogen receptor modulator (raloxifene), calcitonin, denosumab], hormone replacement therapy, and the anabolic agent teriparatide (recombinant human parathyroid hormone 1–34). Anti-resorptive medications increase bone mineral density (BMD) by maintaining existing microarchitecture in osteoporotic bone and reducing bone turnover. Teriparatide (TPTD) increases BMD through formation of new bone and is the only bone formation agent approved by the Food and Drug Administration (FDA). TPTD is administered as a subcutaneous injection 20 μg/day for up to 24 months, and is indicated for the treatment of postmenopausal women with osteoporosis and men with primary or hypogonadal osteoporosis [4].

Maintaining adherence to osteoporosis treatment is essential in achieving optimal therapeutic outcomes [5]. However, previous studies on anti-resorptives (mostly bisphosphonates) have shown that more than half of all patients failed to comply or persist with their medication regimens at 1 year [6–10]. Suboptimal adherence and persistence among patients on anti-resorptive treatment has been linked to an increased risk of fragility fractures [7–12]. For TPTD, a post hoc analysis of the pivotal, randomized clinical trial data reported that longer duration of TPTD decreased the risk of non-vertebral fracture [13]. The association between length of exposure to TPTD and lower risk of fracture has also been reported from observational trials in the USA [14] and in Europe [15]. Similar data on real-world TPTD patients in the USA are lacking, however, as previous research focused on patient characteristics and treatment adherence [16, 17]. Therefore, the aim of this study was to investigate the relationship of fracture risk with treatment adherence and persistence among TPTD patients during a 24-month follow-up period in a US claims database.

Materials and methods

Data source

This study was conducted using Thomson Reuters MarketScan® Research Databases, the Commercial Claims and Encounters Database, and the Medicare Supplemental and Coordination of Benefits Database, for the period of 2004–2008. The Commercial Claims and Encounters Database includes individuals under the age of 65 with a variety of fee-for-service, fully capitated, and partially capitated health insurance plans. The Medicare Supplemental and Coordination of Benefits Database contains individuals age 65 and older with employer-sponsored Medicare supplemental insurance. (Medicare is the US government provided health insurance program for people age 65 or older, under age 65 with specific disabilities, and those with end-stage renal disease.) Services covered by Medicare or the employer-paid portion were both included in the database. Individuals from the two databases were not distinguished in this study and were combined as one study population.

Study population

The study population consisted of new TPTD users aged 18 years and older. New users were defined as having no pharmacy claims for TPTD during the 12 months prior to the first prescription dispensing, and at least two prescription fills with no more than 45 days of gap. The date the first prescription was filled was defined as the index date indicating therapy initiation. Additionally, these new users were required to have continuous enrollment and be eligible for pharmacy benefits during the 12-month pre-index and 24 months post-index period. Patients diagnosed with Paget's disease were identified by International Classification of Diseases (ICD-9-CM) code 731.0 and/or specific medication dosing (alendronate sodium 40 mg daily and risedronate sodium 30 mg daily), and were excluded from the study population.

Baseline patient characteristics, including age and gender, were measured as of index date. Clinical characteristics included assessments of health status, measured by Deyo Charlson Comorbidity Index (CCI) and Chronic Disease Score (CDS), provider specialty, BMD screening, and prevalent fracture observed in the 12-month pre-index period. A prevalent fracture at baseline was defined using the first fracture diagnosis on the medical claim in the pre-index period. Provider specialty was classified as primary care, specialty (i.e., geriatric medicine, obstetrics and gynecology, rheumatology, physical medicine and rehabilitation, and orthopedic surgeons), others, and unknown. Confounding medications included osteoporosis medications (bisphosphonates, raloxifene, calcitonin, hormone replacement) and medications known to be associated with bone loss or risk of fracture (glucocorticoids, hormone deprivation therapy, anticonvulsants, immunosuppressants) [7, 18, 19]. All baseline characteristics were used as covariates in the multivariate regression models. All covariates were categorical variables except for age and CCI which were continuous variables.

TPTD adherence and persistence

Medication adherence was measured by medication possession ratio (MPR). The MPR is the sum of days of supply dispensed during the observation period divided by the total number of days in that period. Given the lifetime maximum exposure of 24 months as indicated in the product labeling,

we limited patient follow-up to 24 months. An MPR greater than or equal to 80% is considered as high adherence and an MPR less than 0.50 is considered as low adherence for osteoporosis medication [5, 7]. We used the same cutoff to define the three levels of TPTD adherence: high adherence (MPR≥0.80), medium adherence (0.50≤MPR<0.80), and low adherence (MPR<0.50).

The days of supply from the pharmacy claims might be overlapped if the patient filled his/her medication before exhausting the previous fill. Therefore, overlapped days of supply were credited before calculating the MPR and persistence. This was done by shifting the later fill date forward to the day after the end of supply of the previous fill.

Medication persistence was measured by the total number of days from the index date until the first 45-day gap. The days of supply of the last prescription was added back in order to capture the whole treatment period, and overlapping days of supply also were credited. Medication persistence was calculated as a continuous variable with mean and standard deviation, and as a categorical variable whereby individual patients were entered into one of four persistence groups: 1–6 months, 7–12 months, 13–18 months, and 19–24 months. Medication persistence categorical variables were used in the descriptive and multivariate regression analyses.

Besides the usual 28-day supply increments (i.e., 28 days/1 month, 56 days/2 months, 84 days/3 months), there were some variations in recorded days of supply (e.g., 30 days, 90 days). In order to avoid recording error and to provide a best estimate of MPR, days of supply less than 28 days were rounded to 28 days, and any other days of supply other than 28, 56, or 84 days were rounded to the nearest 28-day increments. The average MPR and persistence were calculated and plotted at monthly intervals to demonstrate the trend of MPR and persistence as time progressed during the post-index period.

Fractures

Fractures were defined using a claims-based algorithm. A fracture site was determined from ICD-9-CM diagnosis codes at the three-digit level and used only the principal diagnosis code on the medical claim. Fracture sites were categorized as hip, vertebral, and non-vertebral fractures [hip, pelvis, forearm/wrist, clavicle, rib, humerus, upper leg (femur), lower leg (tibia/fibula), ankle, other] (see Appendix). We excluded open fractures, pathologic fractures, and fracture due to trauma, as these are less likely to be related to osteoporosis. Open fractures are typically due to trauma, while pathologic fractures may result from a range of causes other than osteoporosis such as cancer, infection, osteomalacia, Paget's disease, etc. Traumatic fractures were identified either by having an E code for accidents (other than standing height falls) on the same claim, or by having three or more different fractures within 7 days before or after the fracture of interest.

A prevalent fracture was identified using the first diagnosis on the medical claim based on principal ICD-9-CM codes during the 12 month pre-index period. Fractures that occurred after 90 days from index date were considered incident events so as to provide sufficient time for therapeutic effects to begin from TPTD. Incident hip fractures were identified by fracture diagnoses from inpatient admission claims, and subjects were limited to two incident hip fractures. For incident vertebral fractures, identification was made by requiring that a spinal imaging test be conducted within 30 days of the fracture diagnosis. To minimize potential over-counting fractures, only one fracture at each of the individual fracture sites—as determined by the first three-digit ICD-9-CM diagnosis codes was counted during the study period. In addition, re-fractures at the individual three-digit ICD-9-CM level from the pre-index to the post-index, and re-fractures within the post-index period were not included. These decision rules were imposed due to possible reporting of the same fracture event under slightly varying ICD-9-CM codes across medical claims over time. Re-fractures were possible at the aggregate site level for vertebral, hip, and non-vertebral.

Statistical methods

MarketScan® data on the server were queried using PC/SAS code. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for analytic file construction, data manipulation, and statistical analysis. Descriptive statistics for baseline patient characteristics, clinical characteristics, medication use, and previous fracture history were reported for the total study population, the three adherence groups, and the four persistence groups. Mean and standard deviation were reported for continuous variables, and percentage and cell count were reported for categorical variables. The incidence of fractures during the follow-up period, by type, was reported by proportion of patients with fractures and by fracture incidence per 1,000 patient years. Unadjusted comparisons of fractures per 1,000 patient years by MPR and persistence groups were made using chi-square tests.

Logistic regression analysis was performed to assess the association of fracture risk with MPR and persistence after controlling for the same group of baseline covariates. Separate logistic regression models were constructed for each type of fracture—"any clinical", hip, vertebral, non-vertebral fractures—with either MPR or persistence as the exposure variable. Odds ratios (OR), 95% confidence intervals, and associated p values were reported for all the variables included in the logistic regressions, as were the type III analysis of effects for categorical variables with more than two categories. In addition, due to the occurrence of multiple incident fracture events we specified alternative

Poisson regression models using the same covariates to assess the stability of the logistic model results.

Results

There were 3,587 new TPTD users identified in the study population (Fig. 1). The numbers of patients by MPR category were as follows: 1,018 (28%), 842 (23%), and 1,727 (48%) for low, medium, and high, respectively. There were 648 (18%), 593 (17%), 531 (15%), and 1,815 (50%) patients by persistence groups 1–6, 7–12, 13–18, and 19–24 months (Table 1). Average and median lengths of therapy days were 131.8 and 132.5, 312.3 and 327.0, 488.5 and 490.0, and 698.8 and 715.0 for months 1–6, 7–12, 13–18, and 19–24, respectively.

Overall, the mean age was 68.9 years, 91% were female, and 90% were aged 55 and older. Over 71% had a pre-index BMD test, almost 29% had a prevalent fracture, and the majority had prior osteoporosis mediation use within 12 months pre-index date, including 59% with prior bisphosphonate use. There were only a few differences in baseline characteristics across MPR groups. The health status measures [Charlson Comorbidity Index (CCI) and Chronic Disease Score (CDS)] were significantly different across MPR groups, with higher scores (which represent worse health status) in the low MPR group (CCI=1.06; CDS=5.73) and the lowest scores in the highest MPR group (CCI=0.93; CDS=5.27). BMD screening and prior bisphosphonate usage were greater in the high MPR group relative to the low group (74.6% vs. 66.4% and 65.2% vs. 49.4%), while prior use of glucocorticoids was lower in the high MPR group than in the low MPR group (31.2% vs. 36.2%). Similarly, for the persistence categories, CCI and CDS scores were higher in the shortest persistence group, and lowest for the longest persistence group. BMD screening and prior bisphosphonate use was higher in the 19–24-month persistence group (74.7% and 63.9%) compared to the 1–6-month group (68.2% and 48.9%).

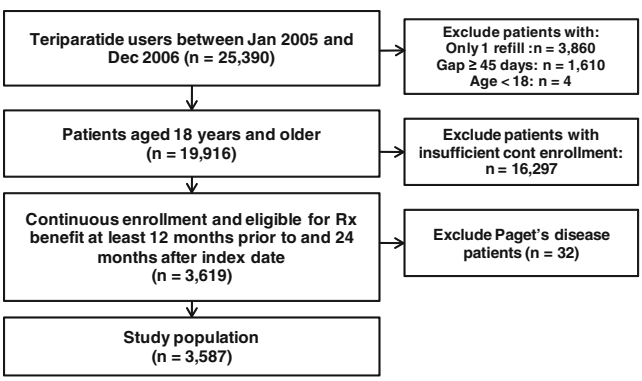

Fig. 1 Patient selection

A gradually decreasing trend was observed for MPR and persistence on therapy over 24 months (Fig. 2). The mean (standard deviation) of MPR at months 6, 12, 18, and 24 was 0.87 (0.16), 0.81 (0.23), 0.75 (0.27), and 0.68 (0.28), respectively. The percentages of patients that were persistent or remained on therapy by end of months 6, 12, 18, and 24 were 85%, 69%, 53%, and 19%, respectively. The average (standard deviation) months of persistence by persistence group was 3.8 (1.63) for 1–6 months, 9.8 (1.73) for 7–12 months, 15.5 (1.69) for 13–18 months, and 22.7 (1.44) for 19–24 months.

The numbers of incident fractures and fractures per 1,000 patient years (PYs) by fracture type and for MPR and persistence groups are shown in Table 2. The proportion of patients with one fracture or with multiple fractures decreased with better MPR for all fracture types. In the low MPR group, for any clinical fracture 13% had an incident event (10% had one fracture; 3% had 2+ fractures), while in the high MPR group 9% had incident fractures (7% had one and 2% had 2+ incident fractures). The unadjusted incidence rate per 1,000 PYs for any clinical fracture ranged from 87.4 (low MPR) to 52.4 (high MPR) ($p<0.05$). For vertebral fractures, the unadjusted incidence rate per 1,000 PYs was 18.2, 12.5, and 6.9 in the low, medium, and high groups, respectively. The high MPR group incidence rates were statistically significantly lower versus the low MPR group. The high MPR group also had a statistically significantly lower incidence rate compared to the low group for non-hip/non-vertebral fractures (38.8 vs. 61.4; $p<0.05$). The patterns were similar by persistence groups. For any clinical fracture, compared to the 1–6 month group (101.1), incidence rates were statistically significantly lower for the 13–18 month (72.5), and the 19–24 month (51.5) groups. Vertebral fracture incidence rates also were lower with longer persistence. Compared to the 1–6 month group, the 13–18 month and 19–24 month groups both had statistically, significantly lower rates. For non-hip/non-vertebral fractures, the incidence rate in the 19–24 month group versus the 1–6 month group was significantly lower (40.2 vs. 66.4; $p<0.05$). For the hip fracture analysis, the proportion of patients with a hip fracture and hip fracture incidence per 1,000 PYs was lower with better MPR and longer persistence, though the unadjusted estimates did not achieve statistical significance.

TPTD MPR, persistence, and fracture risk

The results from the logistic regression models (Table 3) indicated that low MPR, compared to high MPR, was a significant, independent risk factor for any clinical fracture (OR=1.64; $p=0.001$), vertebral fracture (OR=2.56; $p=0.010$), and non-vertebral fracture (OR=1.44; $p=0.029$). Medium MPR was a significant, independent risk factor for

Table 1 Baseline patient characteristics, overall and by MPR and persistence

		MPR				Persistence				
	Total (n=3,587)	Low (n=1,018)	Medium (n=842)	High (n=1,727)	p value	1–6 months (n=648)	7–12 months (n=593)	13–18 months (n=531)	19–24 months (n=1815)	p value
Demographics										
Age	68.96 [11.25]	68.34 [12.25]	68.56 [11.39]	69.52 [10.51]	0.015	68.49 [12.25]	68.23 [11.83]	69.69 [11.25]	69.16 [10.65]	0.092
18–44	1.8% (63)	3.7% (38)	1.3% (11)	0.8% (14)	<0.001	3.7% (24)	2.4% (14)	1.1% (6)	1.0% (19)	<0.001
45–54	8.2% (293)	9.4% (96)	9.3% (78)	6.9% (119)		9.6% (62)	10.5% (62)	7.2% (38)	7.2% (131)	
55–64	26.2% (940)	24.8% (252)	28.1% (237)	26.1% (451)		24.2% (157)	25.6% (152)	25.6% (136)	27.3% (495)	
65–74	28.5% (1,024)	26.7% (272)	27.4% (231)	30.2% (521)		25.9% (168)	29.2% (173)	26.9% (143)	29.8% (540)	
75–84	28.8% (1,033)	28.4% (289)	27.6% (232)	29.6% (512)		29.3% (190)	25.6% (152)	32.0% (170)	28.7% (521)	
≥85	6.5% (234)	7.0% (71)	6.3% (53)	6.4% (110)		7.3% (47)	6.7% (40)	7.2% (38)	6.0% (109)	
Female	91.1% (3,269)	91.7% (934)	90.7% (764)	91.0% (1,571)	0.705	92.3% (598)	91.7% (544)	89.3% (474)	91.1% (1,653)	0.304
Clinical characteristics										
Health status										
Charlson comorbidity index	1.01 [1.44]	1.06 [1.45]	1.11 [1.49]	0.93 [1.39]	0.008	1.12 [1.42]	1.10 [1.54]	1.07 [1.50]	0.92 [1.38]	0.004
Chronic Disease Score	5.48 [3.89]	5.73 [4.10]	5.62 [3.90]	5.27 [3.75]	0.006	5.97 [4.21]	5.49 [3.93]	5.50 [3.95]	5.30 [3.73]	0.002
Provider specialty										
Primary care	46.1% (1,655)	47.5% (484)	48.2% (406)	44.3% (765)	0.232	46.8% (303)	48.4% (287)	47.1% (250)	44.9% (815)	0.848
Specialty	19.8% (712)	20.2% (206)	18.9% (159)	20.1% (347)		19.8% (128)	18.7% (111)	19.6% (104)	20.3% (369)	
Other/unknown	34.0% (1,220)	32.2% (328)	32.9% (277)	35.6% (615)		33.5% (217)	32.9% (195)	33.3% (177)	34.8% (631)	
BMD screening	71.6% (2,570)	66.4% (676)	71.9% (605)	74.6% (1289)	<0.001	68.2% (442)	68.5% (406)	68.9% (366)	74.7% (1356)	0.001
Prevalent fracture	28.5% (1,023)	33.7% (284)	28.4% (239)	29.0% (500)	0.835	27.8% (180)	26.3% (156)	33.3% (177)	28.1% (510)	0.0501
Confounding medication										
Glucocorticoids	33.3% (1,194)	36.2% (369)	34.1% (287)	31.2% (538)	0.02	39.0% (253)	33.6% (199)	30.9% (164)	31.8% (578)	0.005
Hormone deprivation	1.6% (58)	1.6% (16)	1.3% (11)	1.8% (31)	0.648	1.2% (8)	2.0% (12)	1.1% (6)	1.8% (32)	0.523
Anticonvulsants	16.6% (594)	17.7% (180)	18.9% (159)	14.8% (255)	0.016	18.2% (118)	18.2% (108)	15.8% (84)	15.6% (284)	0.289
Immunosuppressants	9.0% (322)	8.7% (89)	9.1% (77)	9.0% (156)	0.949	11.6% (75)	8.6% (51)	8.3% (44)	8.4% (152)	0.087
Other osteoporosis medication use										
Bisphosphonates	58.9% (2,114)	49.4% (503)	57.6% (485)	65.2% (1,126)	<0.001	48.9% (317)	54.5% (323)	59.1% (314)	63.9% (1,160)	<0.001
Raloxifene	13.5% (484)	10.3% (105)	13.3% (112)	15.5% (267)	0.001	11.0% (71)	11.5% (68)	13.7% (73)	15.0% (272)	0.027
Calcitonin	13.2% (473)	12.6% (128)	14.3% (120)	13.0% (225)	0.547	12.0% (78)	13.7% (81)	13.4% (71)	13.4% (243)	0.815
Hormone therapy	18.5% (665)	17.7% (180)	21.4% (180)	17.7% (305)	0.053	19.6% (127)	18.0% (107)	18.6% (99)	18.3% (332)	0.884

Low adherence: medication possession ratio (MPR) <0.5; medium adherence: 0.5≤MPR<0.8; high adherence: 0.8≤MPR. Standard deviations are in square brackets. Numbers of patients are shown in parentheses. p values are for tests of equivalence across adherence or persistence groups

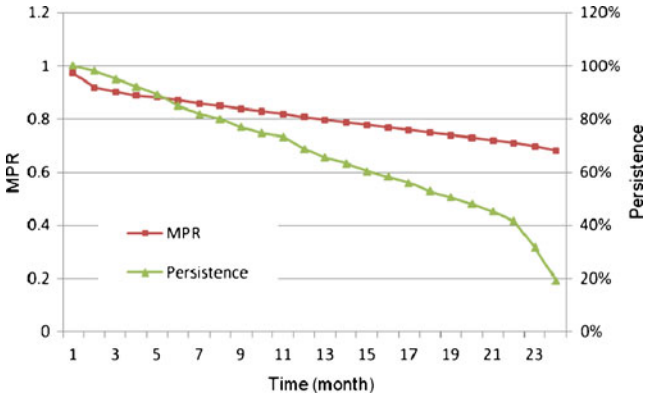

Fig. 2 TPTD MPR and persistence, by month

any clinical fracture (OR=1.49; p=0.035) and non-vertebral fracture (OR=1.45; p=0.036). Patients with low persistence of 1–6 months were much more likely to have any clinical (OR=1.88; p<0.001), vertebral (OR=3.69; p<0.001) or non-vertebral fractures (OR=1.51; p=0.011) when compared to those patients with longer term persistence of 19–24 months. Persistence on TPTD of 7–12 and 13–18 months was associated with lower risk of any clinical fracture (OR=1.41, p=0.027 and OR=1.39, p=0.04, respectively). As in the models using MPR categories, TPTD persistence did not have a statistically significant impact on risk of hip fractures (see Online Resource 1 for full model results.)

The Poisson regression models (see Online Resource 1) revealed similar results to those from the logistic regression models in terms of impact of MPR and persistence on fracture incidence. In the models with MPR covariates, low MPR was associated with greater risk of fracture versus high MPR for any clinical fracture [incidence rate ratio (IRR)=1.61, p<0.001], vertebral fracture (IRR=2.36; p=0.001), and non-vertebral fracture (IRR=1.50; p=0.001). In the persistence models, low persistence of 1–6 months was estimated to increase risk of fracture compared to persistence of 19–24 months for any clinical fracture (IRR=1.83; p<0.001), vertebral fracture (IRR=3.51; p<0.001), and non-vertebral fracture (IRR=1.51; p=0.003). Also, for any clinical fracture, persistence of 7–12 months and 13–18 months had an incidence rate ratio of 1.42 (p=0.007) and 1.33 (p=0.038), respectively, versus persistence of 19–24 months.

Discussion

This study on the impact of MPR and persistence with TPTD therapy on fracture outcomes was conducted using a large administrative claims database in the USA. The present study is the first one performed on TPTD outcomes in patients under real-world clinical practice, and it extends the body of evidence on the potential benefits of longer treatment duration for TPTD. We also examined two measures of therapy exposure—adherence using MPR and persistence. Our results show that fracture risk decreased as either MPR or persistence increased for any clinical, vertebral, and non-vertebral fractures, after controlling for patient characteristics, clinical characteristics, medication use, and previous fracture history.

In our study, fracture incidence per 1,000 patient years decreased with greater TPTD MPR and with longer persistence. In the unadjusted analysis, statistically significant reductions in fracture incidence rates for any clinical and vertebral fractures were estimated for months 13–18 and 19–24 versus 1–6 months. Thus, further reductions in incidence rates were evident beyond 6, 12, and 18 months. In the fully adjusted models, the increase in fracture risk for low-MPR compared to high-MPR TPTD patients was 64%, 156%, and 44% for any clinical, vertebral, and non-vertebral fracture, respectively. In models using persistence groups as the measure of TPTD exposure, short persistence of 1–6 months compared to long persistence of 19–24 months was associated with an 88% increase in risk of any clinical fracture, a 269% increase in vertebral fracture, and a 51% increase of non-vertebral fracture. For any clinical fracture, the risk was significantly higher by 41% and 39% for persistence of 7–12 months and 13–18 months, respectively. Using Poisson regression models, we estimated similar effects from low MPR and short persistence, thus lending further support for the robustness of our findings.

Regarding hip fractures, however, statistically significant reductions were not found in any of our MPR or persistence models using logistic or Poisson regression, perhaps due to the relatively low number of events (n=49). These results may not be surprising given the fact that randomized placebo-controlled clinical trials (RCTs) with hip fracture endpoints generally enrolled between 6,000 and 9,000 patients to detect between group differences [20–22]. Furthermore, hip fracture endpoints have not been studied in teriparatide RCTs, as hip fractures were part of non-vertebral composite endpoints.

The inverse relationship found in this study between therapy exposure and non-vertebral fracture risk is generally consistent with results reported in TPTD randomized clinical trials and prospective observational studies [13–15]. The post hoc analysis of the TPTD pivotal RCT data showed that longer duration of exposure was associated with reduced risk of non-vertebral fractures, where the hazard ratio of TPTD 20 μg/day versus placebo was about 65% at the end of 6 months and decreased 7.6% each month, and by the end of 24 months hazard ratio was about 20% [13]. In the U.S. DANCE observational study, the incidence of new non-vertebral fractures fell from 1.41% during the initial 6 months of treatment to 0.8% during months 19–24 [14]. The risk of

Table 2 Fracture incidence during follow-up, by MPR and persistence

	Incident fracture	Any clinical fracture				Vertebral fracture				Hip fracture				Non-hip/non-vertebral fracture			
		TPTD patients		Fractures		TPTD patients		Fractures		TPTD patients		Fractures		TPTD patients		Fractures	
		N	%	*N*	Per 1,000 PYs	*N*	%	*N*	Per 1,000 PYs	*N*	%	*N*	Per 1,000 PYs	*N*	%	*N*	Per 1,000 PYs
MPR																	
Low	0	879	86%	–	–	983	97%	–	–	1,002	98%	–	–	917	90%	–	–
	1	105	10%	105	–	33	3%	33	–	16	2%	16	–	80	8%	80	–
	2+	34	3%	73	–	2	0%	4	–	0	0%	0	–	21	2%	45	–
		1,018		*178*	*87.4*	*1,018*		*37*	*18.2*	*1,018*		*16*	*7.9*	*1,018*		*125*	*61.4*
Medium	0	735	87%	–	–	823	98%	–	–	832	99%	–	–	758	90%	–	–
	1	89	11%	89	–	17	2%	17	–	10	1%	10	–	74	9%	74	–
	2+	18	2%	37	–	2	0%	4	–	0	0%	0	–	10	1%	21	–
		842		*126*	*74.8*	*842*		*21*	*12.5*	*842*		*10*	*5.9*	*842*		*95*	*56.4*
High	0	1,577	91%	–	–	1,705	99%	–	–	1,705	99%	–	–	1,610	93%	–	–
	1	121	7%	121	–	20	1%	20	–	21	1%	21	–	101	6%	101	–
	2+	29	2%	60	–	2	0%	4	–	1	0%	2	–	16	1%	33	–
		1,727		*181*	*52.4**	*1,727*		*24*	*6.9**	*1,727*		*23*	*6.7*	*1,727*		*134*	*38.8**
Persistence																	
1–6 months	0	546	84%	–	–	617	95%	–	–	635	98%	–	–	577	89%	–	–
	1	77	12%	77	–	30	5%	30	–	13	2%	13	–	58	9%	58	–
	2+	25	4%	54	–	1	0%	2	–	0	0%	0	–	13	2%	28	–
		648		*131*	*101.1*	*648*		*32*	*24.7*	*648*		*13*	*10.0*	*648*		*86*	*66.4*
7–12 months	0	521	88%	–	–	579	98%	0	–	583	98%	–	–	540	91%	–	–
	1	56	9%	56	–	12	2%	12	–	10	2%	10	–	44	7%	44	–
	2+	16	3%	34	–	2	0%	4	–	0	0%	0	–	9	2%	20	–
		593		*90*	*75.9*	*593*		*16*	*13.5*	*593*		*10*	*8.4*	*593*		*64*	*54.0*
13–18 months	0	467	88%	–	–	522	98%	0	–	524	99%	–	–	480	90%	–	–
	1	51	10%	51	–	6	1%	6	–	7	1%	7	–	44	8%	44	–
	2+	13	2%	26	–	3	1%	6	–	0	0%	0	–	7	1%	14	–
		531		*77*	*72.5**	*531*		*12*	*11.3**	*531*		*7*	*6.6*	*531*		*58*	*54.6*

Table 2 (continued)

	Incident fracture	Any clinical fracture				Vertebral fracture				Hip fracture				Non-hip/non-vertebral fracture			
		TPTD patients		Fractures		TPTD patients		Fractures		TPTD patients		Fractures		TPTD patients		Fractures	
		N	%	*N*	Per 1,000 PYs	*N*	%	*N*	Per 1,000 PYs	*N*	%	*N*	Per 1,000 PYs	*N*	%	*N*	Per 1,000 PYs
19–24 months	0	1,657	91%	–	–	1793	99%	–	–	1797	99%	–	–	1,688	93%	–	–
	1	131	7%	131	–	22	1%	22	–	17	1%	17	–	109	6%	109	–
	2+	27	1%	56	–	0	–	0	–	1	0%	2	–	18	1%	37	–
		1,815		*187*	*51.5**	*1,815*		*22*	*6.1**	*1,815*		*19*	*5.2*	*1,815*		*146*	*40.2**
Overall total		3,587		485	67.6	3,587		82	11.4	3,587		49	6.8	3,587		354	49.3

MPR medication possession ratio, *TPTD* teriparatide. Low adherence=MPR<50%; medium adherence: 50%≤MPR<80%; high adherence: >80%. *PY* patient year

*p values <0.05 (versus 1–6 months persistence, or versus low MPR) based on chi-square test on fractures per 1,000 PYs

Numbers in italics are subtotal

Table 3 Logistic regression of likelihood of fracture, by type of fracture, adjusted for TPTD MPR and persistence[a]

TPTD exposure		Any clinical fracture				Vertebral fracture				Hip fracture				Non-vertebral fracture			
		OR	95% CI	*p* value	Type III	OR	95% CI	*p* value	Type III	OR	95% CI	*p* value	Type III	OR	95% CI	*p* value	Type III
MPR	Low	1.64	1.27–2.12	0.000	–	2.56	1.47–4.47	0.001	–	1.17	0.60–2.29	0.642	–	1.44	1.08–1.93	0.013	–
	Medium	1.49	1.14–1.95	0.004	–	1.70	0.91–3.20	0.098	–	0.88	0.41–1.90	0.747	–	1.45	1.08–1.96	0.014	–
	High (reference)	1.00	–	–	<0.001	–	–	–	0.004	–	–	–	0.778	–	–	–	0.014
Persistence	Months																
	1–6	1.88	1.43–2.48	<0.001	–	3.69	2.08–6.53	0.000	–	1.93	0.92–4.06	0.082	–	1.51	1.10–2.07	0.011	–
	7–12	1.41	1.04–1.90	0.027	–	1.90	0.96–3.77	0.067	–	1.75	0.79–3.86	0.167	–	1.22	0.86–1.71	0.263	–
	13–18	1.39	1.01–1.90	0.040	–	1.33	0.60–2.92	0.482		1.20	0.49–2.92	0.691	–	1.37	0.97–1.93	0.077	–
	19–24 (reference)	1.00	–	–	<0.001	1.00	–	–	<0.001	1.00	–	–	0.286	1.00	–	–	0.056

Type III error is the Wald's test and tests for difference between each group

TPTD teriparatide, *MPR* medication possession ratio. Low: MPR<0.50; medium: 0.50≤MPR<0.80; high: MPR≥0.80 (reference). *OR* odds ratio, *CI* confidence interval

[a] Results were adjusted for pre-index covariates for age, sex, geographic region, health insurance plan type, health care provider type, Charlson comorbidity index, bone mineral density (BMD) screening, use of osteoporosis and other medications associated with bone loss and fracture risk, and prevalent fracture

clinical fractures in the European Forsteo Observational Study (EFOS) was shown to decline over time, as the odds ratio of fracture in TPTD patients was 0.68 and 0.53 for months 6–12 and 12–18, respectively, compared to treatment within the first 6 months [15].

Our estimates of MPR are higher than those from previous reports, while our persistence estimates are comparable. Our MPR estimates were 87%, 81%, and 68% at months 6, 12, and 24 months, whereas Foster and colleagues [17] reported 74%, 66%, and 58%. These differences are likely due to the inclusion criteria used. We excluded those patients with only one TPTD prescription and we required continuous enrollment criteria of 12 months pre-index and 24 months post-index. Foster and colleagues [17] included patients with only one TPTD prescription and their continuous enrollment requirement was 12 months pre-index but imposed only a minimum of 180 days follow-up post-index. The exclusion of single prescription patients naturally raises the MPR for the remaining sample. Our estimates on persistence were quite similar to those from EFOS. At 6 and 12 months, Langdahl and colleagues [15] reported persistence of 87.7% and 77% compared to our 85% and 69%; and in both studies there was a similar steep rate of discontinuation as the allowable treatment maximum (18 months in Europe; 24 months in the USA) was approached.

The estimates of fracture risk reductions associated with MPR and persistence reported here are larger than those from similar studies on anti-resorptive therapies (mostly bisphosphonates). A recent study on adherence (based on MPR) of bisphosphonate therapies among patients using a large US claims database showed a 37% increase in fracture risk among low-MPR patients relative to high-MPR patients [10], while in our study we found a 64% increased risk of any fracture among low-MPR patients. Reviews of the literature indicated that good compliance (MPR≥80%) over 2 years reduced the risk of fracture by about 20–30% [6, 23], while non-persistence generally increased fracture risk by 30–40% [23]. However, any comparisons between the current study and similar research on other osteoporosis therapies should consider the following caveats. TPTD is a daily injection and compliance and persistence would be expected to be a more formidable challenge relative to oral therapies or longer intervals of dosing such as weekly or monthly oral therapy, semi-annual injection, or annual infusion. Unobserved individual attitudes, beliefs, and motivations to remain on a daily injection may differ vis-à-vis those of patients on other osteoporosis therapies. Another consideration should be the underlying risk profile of patients prescribed TPTD compared to anti-resorptive therapies. Many clinical guidelines call for use of bisphosphonates or other osteoporosis medications before granting access and reimbursement for TPTD. Our analysis found that about 60% had previous bisphosphonate use and over 25% had used other anti-resorptive therapies in the 12 months prior to initiation of TPTD. There may be selection bias between TPTD patients and patients on anti-resorptives that may not be accounted for in comparisons between studies. Another important caveat is that fracture efficacy for anti-resorptives has been established mostly from 36-month RCTs, while for TPTD the median duration of therapy was 19 months in the pivotal RCT [24].

There are a number of important limitations to our study that warrant further discussion. As a retrospective secondary analysis of medical and pharmacy claims data, this study bears all the inherent limitations such as potential miscoding the fracture type or over- or under-estimating the fracture incidences. We imposed algorithms to identify prevalent and incident fractures to screen out cases that may not have been legitimate. Although these algorithms were developed in consultation with medical and scientific experts, their validity and reliability have not yet been established. We also adjusted for all key available confounding factors, including age, gender, health status, BMD screening, prior fracture, and medication use. However, other clinical risk factors for osteoporosis such as race, family history, BMD T-scores, eating disorders, low calcium intake, tobacco use, sedentary lifestyle, and excessive alcohol consumption were not available in the claims database. The incomplete control for these confounding factors could lead to potential residual confounding and result in biased estimates of the association of fracture risk with therapy MPR and persistence.

Certain medical conditions like serious kidney failure, hyperparathyroidism and hyperthyroidism, rheumatoid arthritis, and diabetes can also interfere with bone formation or cause bone loss. Usually, treatment of secondary osteoporosis is more complex than treatment of primary osteoporosis and depends on the underlying disease. Not controlling for these diseases that might cause secondary osteoporosis could have attenuated the association of fracture incidence with MPR and persistence.

Patient adherence was measured by MPR, which was based on administrative prescription claims. However, we cannot ascertain proper injection of the medication nor the dose patients actually received. Moreover, the MPR was calculated as the sum of days of supply during the fixed 24-month post-index period for every patient in order to capture the total amount of exposure to TPTD. However, it is possible that some patients might be highly adherent to the treatment but discontinued the medication early. In this case, those patients would have a low MPR based on our calculation. Also, we defined persistence as continuation of the treatment period until the first 45-day gap. Those patients with low persistence were predetermined to be poorly adherent, despite their actual adherence during

treatment period. Therefore, our MPR calculation could have introduced additional correlation between MPR and persistence. This likely contributes to the similar covariate estimates in both MPR and persistence models.

We restricted our study sample to new TPTD starters with at least two prescription fills and less than 45 days' gap between two fills. This exclusion increases the overall MPR and persistence estimates. The single TPTD patients were excluded because such minimal exposure, if any, would not be expected to yield outcomes that reflect those from patients with typical TPTD exposure. Of the 3,860 single TPTD patients excluded from the analysis, only 515 would have met the age, continuous enrollment, and absence of Paget's disease inclusion criteria. A comparison of this single prescription group to the included patient sample revealed differences in baseline characteristics for age (70.6 vs. 68.9, $p<0.01$), CCI (1.28 vs. 1.01; $p<0.001$), BMD screening (59% vs. 71.6%; $p<0.001$), and pre-index period bisphosphonate use (44.3% vs. 58.9%; $p<0.001$) (see Online Resource 1). More importantly, during the post-index follow-up period, the single prescription group had a higher rate of any clinical fracture per 1,000 PYs (95.1 vs. 67.6; $p<0.01$). The inclusion of this single TPTD prescription group most likely would have led to higher odds ratios for the low MPR and short persistence covariates in the regression models.

Lastly, our predefined analysis on the impact of persistence was based on 6-month intervals and does not formally address the question on what is the cumulative number of months of TPTD exposure whereby the incremental clinical benefits may become insignificant. In order to gain some insights on this question, an exploratory analysis was performed whereby the month 19–24 variable was split into a month 19–21 and month 22–24 variable (as the referent group) in the any clinical fracture model. The odds ratio for the month 19–21 variable was not statistically significant, suggesting that additional fracture risk reduction may plateau during months 19–21 of exposure versus 22–24 months (see Online Resource 1). However, it is not clear what clinical recommendations can or should be made from these exploratory results, particularly if therapeutic benefits are sustained after therapy termination and such sustained benefits are proportional to the total length of exposure to TPTD [25]. A new analysis of TPTD patients using longer post-therapy follow-up would be necessary to properly address this question, but is beyond the scope of this study.

Conclusion

The current study is the first to investigate the relationship between MPR and persistence of TPTD and fracture risk in patients in real-world clinical practice in the USA. Using a large administrative claims database, TPTD patients were observed for two years after therapy initiation. Longer persistence and better adherence, as measured by MPR, to daily injection TPTD were found to be associated with significant reductions in the risk of any clinical, vertebral, and non-vertebral fracture. Given the substantial clinical benefits, increased attention should be given to improve patient adherence and persistence to therapy.

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Appendix

Table 4 Codes for diagnosis of fractures

Fracture	ICD-9-CM diagnosis
Vertebral	805.2, 805.4, 805.6, 805.8, 806.2x, 806.4, 806.6x, 806.8
Non-vertebral	
Hip	820.0x, 820, 820.01, 820.02, 820.03, 820.09, 820.2, 820.21, 820.22, 820.8
Clavicle/rib	807.0x, 807.2, 810.0x
Pelvis	808, 808.2, 808.4x, 808.8
Humerus	812.0x, 812.2x, 812.4x
Wrist/forearm	813.0x, 813.2x, 813.4x, 813.8x
Upper leg	821, 821.01, 821.2, 821.21, 821.22, 821.23
Lower leg	823.0x, 823.2x, 823.4x, 823.8x
Ankle	824, 824.2, 824.4, 824.6, 824.8
Other	822, 811.0x, 818, 825, 825.2x

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