ORIGINAL RESEARCH

Long-Term Effects of Teriparatide Followed by Antiresorptive Therapy on Clinical Outcomes in Patients with Severe Spinal Osteoporosis

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Abstract

Teriparatide (TPTD) is the most widely used anabolic agent in the treatment of patients with osteoporosis although its use is restricted in many countries. A recent randomised trial confirmed that TPTD was superior to risedronate at preventing vertebral fractures over a 2-year period. There is limited information on the relative effectiveness of TPTD compared with standard care in routine clinical practice. In this paper, we report the results of an extended observational study of 724 women referred to a specialist clinic with severe osteoporosis over an 11.5-year period, who were considered for TPTD therapy. Of these patients, 496 (68.5%) were treated with TPTD, whereas the remaining 228 (31.5%) received other treatments. This was either because they were unwilling or unable to self-inject (52.6%), because they had already been established on oral bisphosphonates (31.1%) or because of contraindications (12.7%). The TPTD group were younger than the standard care group (69.6 vs. 74.1 years) and had a lower 10-year fracture risk (25.7% vs. 28.6%). Those treated with TPTD had a greater increase in BMD at the lumbar spine compared with standard care (13.3% vs. 8.2%, $p < 0.001$) after approximately 2 years and had a lower incidence of vertebral fractures (4.8% vs. 10.1%, $p = 0.01$) over the course of our observation. There was no difference between groups with respect to either BMD change at the femoral neck or incidence of non-vertebral fractures. This study confirms that TPTD is superior to standard care at reducing the risk of vertebral fracture in patients with severe osteoporosis.

Keywords Postmenopausal osteoporosis · Teriparatide · Observational study

Introduction

Teriparatide (TPTD) is an anabolic agent which has been shown to reduce the risk of both vertebral and non-vertebral fractures in postmenopausal women compared to placebo [1]. Teriparatide has also been shown to reduce the risk of vertebral fractures compared with oral alendronate in glucocorticoid induced osteoporosis and risedronate in postmenopausal osteoporosis [2–5].

While randomised controlled trials (RCTs) are generally considered to be the gold standard for assessing the effects of new treatments [6], it is widely recognised that patients who take part in such trials are not representative of those being treated in routine clinical practice due to stringent inclusion and exclusion criteria. This was demonstrated in a trial of 120 newly diagnosed osteoporotic female patients attending a referral centre in the USA, who were felt to be suitable candidates for therapy. However, only 3–21% of patients would have been eligible to take part in ongoing trials, mainly due to co-morbidity or concomitant medications [7]. Observational studies can therefore provide important information to complement the results of RCTs and their applicability to routine practice.

Our previous study, involving 323 patients followed up over a 5-year period, demonstrated TPTD was superior to standard care at reducing the risk of vertebral fractures in severe osteoporosis [8]. We have now extended this study to involve 724 patients followed up over an 11.5-year

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period and have analysed changes in BMD and occurrence of fractures both during TPTD therapy and afterwards, following the introduction of antiresorptive therapy. The current study includes women from the initial study, but excludes 27 men. This reflects changes in prescribing from 2008 onward necessitated by SMC guidance which did not recognise the use of TPTD in male osteoporosis.

Patients and Methods

Study Population

The study group comprised of 724 women who had been referred to a specialist clinic in NHS Lothian because of severe osteoporosis (defined as a T-score of equal or less than −4.0 at the lumbar spine) between 2005 and 2016. The enrolment period was from February 2005 to July 2016. Within this cohort, all patients were included in the fracture analysis and those with a duration of follow-up of more than 12 months were included in the BMD analysis (with the exception of one patient with a new diagnosis of coeliac disease who did not receive any specific treatment for osteoporosis).

The policy of the specialist clinic was to offer patients with a T score of −4.0 or less TPTD therapy unless there was a contraindication, or they had already been stabilised on bisphosphonate therapy for 2 months or more.

Baseline Assessment

At the initial clinic visit, information was gathered as part of normal clinical care including; past medical history, previous and current medications, family history, alcohol intake, smoking status, and history of fractures. Blood tests were taken to measure urea and electrolytes, serum $25(OH)D_3$ level, serum albumin and calcium. A 10-year fracture risk was calculated using the FRAX algorithm for each patient [9]. All patients underwent measurements of bone mineral density (BMD) at the lumbar spine, total hip and femoral neck using a Hologic QDR 4500 densitometer. Lumbar spine values were based on the average of L1–L4 unless individual vertebra had been affected by fracture or other artefacts such as osteoarthritis (and if so, the average was based on evaluable vertebrae). The short term precision has been estimated at 1.3% for spine, 1.2% total hip and 1.4% for femoral neck, and long-term precision estimated at 2.4% for lumbar spine, 2.3% for total hip and 2.7% for femoral neck. The manufacturer (Hologic) supplied reference population based on over 50,000 DXA

observations in the US population was used for calculating T scores.

Follow-Up

Patients were typically reviewed at 4 months and 12 months after commencing treatment. At each review, they were asked about adherence to medications, fractures and adverse effects. Those who had received TPTD were transferred to an antiresorptive agent at the end of TPTD treatment (either 18 or 24 months). Further reviews were performed 5 years after commencing therapy.

Measurements of bone mineral density (BMD) at the lumbar spine, total hip and femoral neck were repeated on the same machine after about 12 months and 24 months with the exception of patients who underwent an 18-month course of therapy in which case the scans were performed at 9 and 18 months. Additional scans were performed at about 5 years after commencing therapy. Bone turnover markers were not performed routinely in this service.

Patients were asked about their fracture history at each clinic review. All fractures were confirmed by x-ray or other imaging by radiologists who were independent of the care team. Each patient's electronic record was also reviewed retrospectively to identify any fractures that were not mentioned at clinic review. All fractures were recorded, but the final analysis included only the most common non-vertebral fractures specified by the US Food and Drug Administration (FDA) [10], or major fractures specified by the European Union Committee for Medicinal Products for Human Use (CHMP) [11]. Facial, metacarpal, finger and toe fractures have been excluded from analysis in this study.

Statistical Analysis

Statistical analysis was performed using Minitab version 15 (Minitab, State College, PA). Differences between groups were assessed either by t test for continuous variables or by Chi square test for categorical variables. Propensity scores were generated in SPSS version 22 (IBMM, Armonk, NY) entering age, sex, height, weight, smoking status, current glucocorticoid use, alcohol (3 or more units/day), rheumatoid arthritis, secondary osteoporosis and femoral neck BMD as predictors of treatment allocation. Sensitivity analyses were performed using regression modelling entering treatment allocation as a categorical variable and either age and BMI or propensity score as continuous variables. Analysis was by intention to treat and patients were not excluded if they either died during treatment or stopped treatment prematurely.

Results

Characteristics of the Study Population

The characteristics of the TPTD and standard care groups are illustrated in Table 1. The baseline T score at the lumbar spine was similar in both groups. However, those in the standard care group had a significantly lower baseline T score at the femoral neck and hip, compared to the TPTD group. The proportions of patients with a previous fracture were similar in both groups. Whilst the majority of patients were treatment naïve, 12.5% of patients in the TPTD group had failed to respond to a previous treatment, compared to 6.6% in the standard care group ($p = 0.01$). This was defined as a fall in BMD of more than 4% and the occurrence of a fragility fracture, or the occurrence of more than one fragility fracture despite adherence to therapy.

Patients who were treated with TPTD were significantly younger than those treated with standard care (69.6 years vs. 74.1 years, $p < 0.001$). A higher proportion of those in the standard care group had a history of cardiovascular disease (21.9% vs. 12.1%, $p = 0.001$) and previous malignancy (12.3% vs. 3.0%, $p < 0.001$). A total of 124 patients (17.1%) died during the study with death equally likely to occur in both groups. A higher proportion of the TPTD group had a history of parental hip fracture (18.4% vs. 11.4%, $p = 0.02$). The 10-year fracture risk, as determined by FRAX, was significantly higher in the standard care group than TPTD group (28.6% vs. 25.7%, $p < 0.001$). There was no significant difference between groups in terms of body mass index, serum creatinine, serum $25(OH)D_3$, previous treatments, smoking status, alcohol intake and glucocorticoid use.

Treatments Received

The treatments received in the teriparatide and standard care groups are shown in Table 2. Teriparatide was prescribed at a dose of 20 μg daily by patient administered subcutaneous injection. Between 2005 and June 2008, the treatment duration was 18 months and thereafter treatment duration was 24 months due to changes in the UK product licence. Following completion of TPTD therapy, patients were offered anti-resorptive therapy according to usual standard clinical practice (see Table 2). Patients in the standard care group received a variety of therapies as shown in Table 1. Both groups of patients were also routinely co-prescribed calcium and vitamin D supplements at doses of 1,000 mg calcium and 800U vitamin D daily.

The reasons for not receiving TPTD in the standard care group were patient declined ($n = 84$, 36.8%), already stabilised on another treatment ($n = 71$, 31.1%), unwilling or unable to self-inject ($n = 36$, 15.8%), unknown reason ($n = 8$, 3.5%) or contraindication ($n = 29$, 12.7%). The contraindications included impaired renal function ($n = 6$), previous malignancy ($n = 7$), previous radiotherapy ($n = 11$) or hyperparathyroidism ($n = 5$).

Follow-on Therapy

The follow-on therapy for patients treated with teriparatide is illustrated in Table 3 ($n = 395$). No follow-up therapy information was available for patients who died whilst on TPTD treatment ($n = 7$, 1.4%), or who had not completed their course of TPTD ($n = 94$, 19.0%).

Response of BMD

The follow-up data for the response of BMD in both groups is displayed in Table 4. There was a significantly greater increase in the spine BMD in the TPTD group compared with the standard care group (7.2%/year vs. 4.4%/year, $p = 0.00$). There was no significant difference between groups in the BMD response at the femoral neck. There was a similar interval between scans in both groups (23.0 months vs. 22.3 months, $p = 0.30$). Sensitivity analyses were performed to examine the role of potential confounders in view of the observational nature of this study. Teriparatide remained a highly significant predictor of improved BMD even after adjustment for age and body mass index, as well as after adjustment for treatment allocation propensity scores.

Bone mineral density changes at the spine and femoral neck were analysed at different time intervals following the initiation of treatment, as displayed in Fig. 1. In both groups, the greatest BMD increases were noted in the spine occurring within the first 12 months of treatment. In the TPTD group, spine BMD increased by 10.46% in the first year of treatment ($n = 223$), compared with a 5.27% increase in the standard care group ($n = 59$). After a further year of TPTD the cumulative gain in spine BMD had reached 12.99% ($n = 223$), compared to 8.60% in the standard care group ($n = 48$). Modest increases in bone mineral density at the femoral neck were observed with no significant differences between the TPTD and standard care groups. In the TPTD group, femoral neck BMD increased by 1.39% in the first year of treatment ($n = 224$), compared with a 1.86% increase in the standard care group ($n = 58$). After a further year of TPTD the cumulative gain in femoral neck BMD had reached 3.1% ($n = 223$), compared to 3.7% in the standard care group ($n = 49$). Follow-up data after 5 years is available in a small number of the participants with the absolute changes in BMD appearing broadly similar to

Table 1 Characteristics of the teriparatide (TPTD) and standard care groups

	TPTD (n=496)	Standard care (n=228)	p value
Demographics			
Age (Years)	69.6±9.9	74.1±9.1	<0.001
Baseline investigations			
Lumbar spine T score	−4.3±0.7	−4.4±0.6	0.08
Femoral neck T score	−3.0±0.8	−3.2±0.8	<0.001
Hip T score	−2.7±0.9	−3.1±0.90	<0.001
Body mass index (kg/m^2)	23.3±4.2	22.9±4.1	0.16
Serum creatinine (μM/L)	66.4±14.2	69.7±22.2	0.04
Serum 25 (OH)D$_3$ (nM/L)	57.2±35.8	57.0±33.3	0.90
Previous fractures			
Any fracture	421 (84.9%)	198 (86.8%)	0.48
Vertebral fracture	273 (55.0%)	117 (51.3%)	0.35
Multiple vertebral fractures[a]	171 (34.5%)	78 (34.2%)	0.94
Previous treatments[b]			
No treatment	285 (57.4%)	120 (52.6%)	0.23
Bisphosphonates[c]	155 (31.2%)	86 (37.7%)	0.09
Calcium/vitamin D[d]	163 (32.8%)	91 (39.9%)	0.07
Indication for treatment			
Postmenopausal osteoporosis	458 (92.3%)	212 (93.0%)	0.76
Severe osteoporosis[e]	405 (81.6%)	189 (82.9%)	0.69
Resistant to therapies[f]	62 (12.5%)	15 (6.6%)	0.01
Morbidities			
Chronic obstructive pulmonary disease	81 (16.3%)	40 (17.5%)	0.68
Cardiovascular disease	60 (12.1%)	50 (21.9%)	0.001
Diabetes mellitus	15 (3.0%)	9 (3.9%)	0.52
Malignancy	15 (3.0%)	28 (12.3%)	<0.001
Death	84 (16.9%)	40 (17.5%)	0.5
Other factors			
Smoker	99 (19.9%)	44 (19.3%)	0.85
Alcohol (units/week)	3.2±5.7	2.5±7.4	0.25
Glucocorticoid use	34 (6.9%)	18 (7.9%)	0.62
Rheumatoid arthritis	35 (7.1%)	19 (8.3%)	0.55
Parental hip fracture	91 (18.4%)	26 (11.4%)	0.02
10-year fracture risk % (FRAX)	25.7±11.6	28.6±12.8	<0.001
10-year hip fracture risk % (FRAX)	12.5±10.5	15.9±12.9	<0.001

p values refers to difference between groups by t test or Chi square test

[a]Defined as two or more

[b]Other previous treatments included TPTD: Strontium 7, Calcitonin 1, Raloxifene 6, Hormonal replacement therapy (HRT) 16. Standard Care: Strontium 1, Raloxifene 1, H 1

[c]Bisphosphonates includes TPTD: Alendronate 113, Risedronate 35, Zoledronate 3, Ibandronate 3. Standard Care: Alendronate 70, Risedronate 16, Zoledronate 1, Ibandronate 1. All co-prescribed with calcium and vitamin D supplements

[d]Prescribed in the absence of any other osteoporosis medication

[e]Severe osteoporosis defined by bone mineral density T score of −4 or less at the spine or hip

[f]Failure to respond to therapy defined as the occurrence of more than one fracture despite therapy adherence or a decline in BMD and at least one fracture despite therapy adherence

those achieved at 2 years. Perhaps due to reduced numbers of participants and variation in treatment responses these differences did not reach statistical significance at either site (spine BMD gain of 12.8% with TPTD (n=48) compared to 8.15% with standard care (n=23), femoral neck BMD gain of 1.1% with TPTD (n=49) compared to 0.24% with standard care (n=26).

Table 2 Treatment regimens in teriparatide and standard care group

Teriparatide (n = 496)		Standard care (n = 228)	
Treatment regimen	Number (%)	Treatment regimen	Number (%)
18 months of therapy (20 μg daily subcutaneous injection)[a]	96 (19.4%)	Alendronate[a]	159 (69.1%)
		Zoledronic acid[a]	30 (13.0%)
24 months of therapy (20 μg daily subcutaneous injection)[a]	400 (80.6%)	Risedronate[a]	17 (7.4%)
		Other treatments[b]	22 (9.6%)

Details of treatment regimens; Alendronate (oral 70 mg once weekly), Zoledronic acid (intravenous 5 mg annually), Risedronate (oral 35 mg once weekly), Denosumab (subcutaneous 60 mg 6 monthly), Strontium ranelate (oral 2 g once daily). In accordance with standard practice in the UK, oral bisphosphonates were prescribed for 5 years, at which stage a repeat bone density scan was performed. If at this point BMD values were in the osteoporotic range, then treatment was continued for 10 years. Intravenous zoledronate was given as 3 annual infusions followed by a 3-year drug holiday. Denosumab was offered for 5 years in the first instance

[a]Note all of the above were co-prescribed calcium and vitamin D, once daily

[b]Other treatments include denosumab (n = 8, 3.5%), calcium/vitamin D alone (n = 4, 1.7%), Strontium ranelate (n = 2, 0.8%), unknown (n = 8, 3.5%)

Table 3 Follow-on therapy after course of Teriparatide treatment (n = 395)

Follow-on therapy after Teriparatide	Number of patient (%)
Alendronate[a]	213 (53.9%)
Risedronate[a]	18 (4.5%)
Zoledronic Acid[a]	117 (29.6%)
Other treatment[b]	35 (8.9%)
No treatment	9 (2.3%)
Not known	3 (0.8%)

Details of treatment regimens: Alendronate (oral 70 mg once weekly), Zoledronic acid (intravenous 5 mg annually), Risedronate (oral 35 mg once weekly), Denosumab (subcutaneous 60 mg six monthly), Strontium ranelate (oral 2 g once daily)

[a]Co-prescribed Calcium (1000 mg) and Vitamin D (800 units) daily

[b]Other treatment includes; Denosumab (n = 27, 5.5%), Calcium/vitamin D alone (n = 5, 1.0%), Strontium ranelate (n = 1, 0.2%), Hormonal replacement therapy (n = 1, 0.2%), further course of TPTD (n = 1, n = 0.2%)

Fractures

In the TPTD group, the proportion of patients with vertebral fractures was fewer than in the standard care group (4.8% vs. 10.1%, p = 0.01), as illustrated in Table 5. This difference remained statistically significant after adjusting

for baseline FRAX score, and for treatment allocation propensity scores. The duration of follow-up was similar in both groups (53.8 vs. 54.4 months, p = 0.86). The difference in multiple vertebral fractures (1.8% vs 3.9%, p = 0.09) was not statistically significant.

There was no difference between groups in terms of non-vertebral fracture. In the TPTD group, a total of 133 non-vertebral fractures were sustained, in 105 individuals (21.2%). The majority of these were at the hip (n = 30, 6.1%) and wrist (n = 31, 6.3%). Others included humerus (n = 14, 2.8%), rib/clavicle (n = 8, 1.6%), ankle (n = 10, 2.0%), pelvis (n = 13, 2.6%) and other sites (n = 27, 5.4%). Six fractures were excluded from analysis. In the standard care group, a total of 55 non-vertebral fractures occurred in 49 women (21.5%). The majority of these were at the hip (n = 15, 6.6%), wrist (n = 10, 4.4%) or pelvis (n = 11, 4.8%). Other fractures included humerus (n = 4, 1.8%), ribs/clavicle (n = 7, 3.1%), ankle (n = 4, 1.8%) or other sites (n = 4, 1.8%). Four fractures were excluded from analysis.

Discussion

Teriparatide is approved for the restricted treatment of severe osteoporosis in postmenopausal women. The anabolic mechanism of action is distinctly different from the anti-resorptive effects of bisphosphonates, which are the mainstay of treatment for osteoporosis. In the United Kingdom, the use of TPTD is restricted to certain patient groups due to guidance from regulatory bodies including the National Institute of Clinical Excellence (NICE) [12], the Scottish Medicines Consortium (SMC) [13], and the Scottish Intercollegiate Guidelines Network (SIGN) [14]. Current NICE guidelines suggest TPTD is recommended as an alternative treatment option in postmenopausal women for secondary prevention of osteoporotic fractures under the following conditions: patients must be aged 65 or over with a T score of −4.0 or less (or a T score of −3.5 or less with more than two previous fractures, or aged 55–64 with a T score of −4.0 or less plus more than two previous fractures) and unable to take oral bisphosphonates or strontium ranelate (due to contra-indications or intolerance) or have an unsatisfactory response to oral bisphosphonate [12]. The Scottish Medicine Consortium (SMC) guidance suggests TPTD therapy is acceptable for use in severe osteoporosis for postmenopausal women, under specialist use. In 2008, the SMC stated it did not recommend TPTD for the treatment of osteoporosis in men [13]. Based on SMC advice and the SIGN guidance, TPTD is predominantly used by specialists in Scotland for the treatment of severe osteoporosis in postmenopausal women.

Table 4 Bone Mineral Density (BMD) changes in the study population

	TPTD ($n=314$)	Control ($n=83$)	p value	p value (adjusted age/BMI)	p value (adjusted p value Score)
Scan Time (Months)	23.0 ± 5.1	22.3 ± 6.4	0.30	0.50	0.61
Change in lumbar spine BMD (%)	13.3 ± 8.8	8.2 ± 8.7	0.00	0.00	0.00
Change in femoral neck BMD (%)	3.0 ± 9.9	3.3 ± 7.1	0.78	0.70	0.67
Change in lumbar spine BMD (%/year)	7.2 ± 5.2	4.4 ± 4.9	0.00	0.00	0.00
Change in femoral neck BMD (%/year)	1.5 ± 5.1	2.0 ± 4.0	0.50	0.43	0.45

Based on longest scan interval performed between months 12 and 36 after baseline visit. Values are mean ± standard deviation, unadjusted p values refer to difference between groups by t test, adjusted p values refer to significance attributable to teriparatide as a categorical predictor of outcome in regression models incorporating age and BMI or propensity scores, respectively

Teriparatide has demonstrated effectiveness in randomised clinical trials in terms of improving bone mineral density and reducing fracture incidence compared to placebo [1]. Comparative studies with bisphosphonates have also illustrated a superior effect of TPTD in improving bone mineral density and reducing the risk of vertebral fractures in postmenopausal osteoporosis and glucocorticoid-induced osteoporosis (noting that Body et al. used a higher daily dose of teriparatide) [2–4, 15]. The VERO study compared TPTD with risedronate in a population of 1360 women using incidence fractures as the primary outcome. The study indicated that the fracture risk in patients receiving TPTD was significantly lower than that of the patients receiving risedronate [5]. A recent meta-analysis of six randomised trials comparing TPTD to alendronate reiterated that TPTD therapy is associated with a greater increase in lumbar spine BMD [16].

There exist little data describing the effectiveness of TPTD out with a randomised controlled trial setting. We previously reported an observational study, in which we reviewed the clinical outcome for patients with severe osteoporosis treated with either TPTD or standard care over around 5 years. We identified that in a total population of 323 patients, TPTD was superior in preventing new vertebral fractures and improving spine BMD, compared to standard care, in routine clinical practice [8].

Here, we have extended this study considerably. Not only was the sample size greater, but we also analysed the long-term response following introduction of antiresorptive therapy. The present study showed that patients treated with TPTD had a significantly greater increase in BMD at the spine, compared with standard care. There was no significant difference between groups in terms of the change in femoral neck BMD or total hip BMD. These findings are in keeping with previous randomised controlled trials comparing TPTD and bisphosphonates [2–5] and are also similar to our previous study in which we observed an 8.2%/year increase in spine BMD with TPTD and a 5.0%/year increase with

standard care [8] compared with 7.2%/year in the TPTD group and 4.4%/year in the standard care group in the present study.

Those treated with TPTD therapy had a lower incidence of vertebral fractures compared to those treated with standard care (4.8% vs, 10.1%, $p = 0.01$), but there was no significant difference in the incidence of non-vertebral fractures. This is, again, in keeping with our previous findings [8]. We observed a slightly higher vertebral fracture incidence in both groups in this analysis, which is likely due to the longer follow-up period (53–54 months). Randomised comparative trials have also shown superiority of TPTD over bisphosphonates in preventing vertebral fractures but yielding no significant difference in non-vertebral fractures. For example, in the VERO trial of 1360 women treated with either TPTD or risedronate, vertebral fracture rate was 5.4% in the TPTD group and 12% in the risedronate group ($p = <0.0001$), whereas the incidence of non-vertebral fragility fractures was 4.0% vs 6.1% ($p = 0.10$) [5].

We also analysed the effect on bone mineral density following cessation of TPTD by which point most patients had received anti-resorptive therapy with bisphosphonates. As expected, the greatest gain in BMD occurred in the first 12 months of treatment, with gains over the first 2 years also significantly higher in the TPTD treated group. Although the absolute change in bone density remained very similar in those patients followed up for 5 years, the difference was no longer significant presumably due to greater variation in BMD seen and the much smaller number of patients in whom this data was available.

The study has several limitations. It was an observational study and therefore allocation to treatments was not randomised. As a reflection of this fact, patients treated with standard care were older, had a higher femoral neck T-score, had a history of malignancy and had lower serum creatinine levels than those receiving TPTD. This indicates that in routine practice, older, more frail individuals
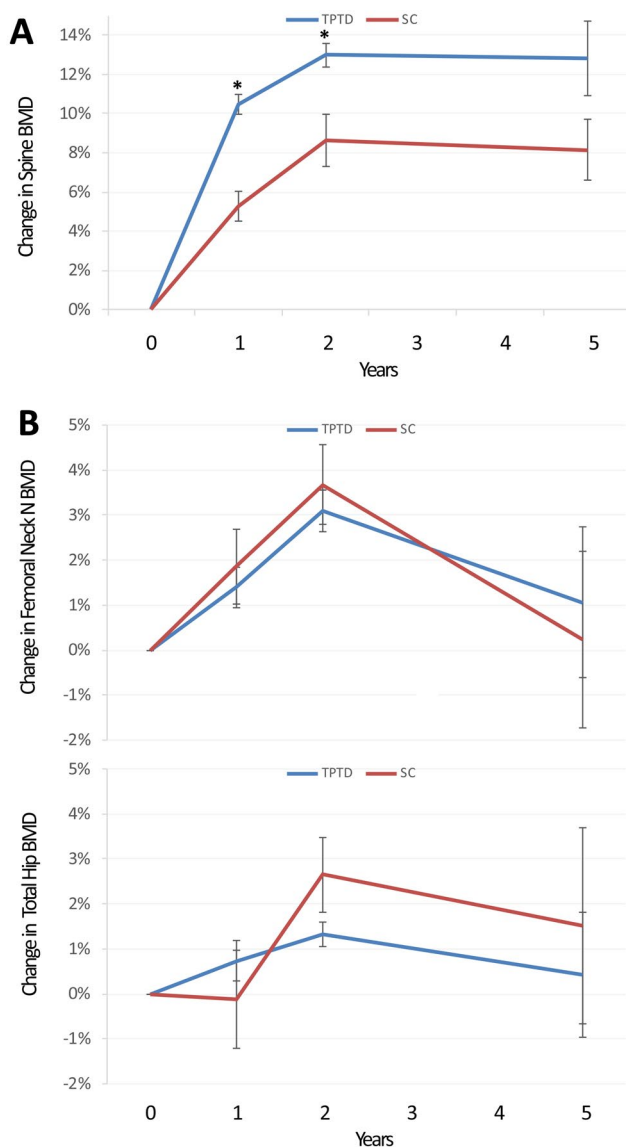
might elect not to have TPTD therapy. It is also not possible to accurately assess patient compliance in either group and therefore we are unable to exclude the possibility that the favourable result with TPTD may be related to compliance. In terms of monitoring bone mineral density, we did not have repeat scans for all patients at the desired time interval, resulting in a reduced study power. Finally, we did not systematically gather information on side effects; however, we can report that there were no major adverse events of symptomatic hypercalcaemia, osteonecrosis of the jaw or atypical femoral fractures in either treatment group.

However, the strength of this study is that it provides information regarding the use of TPTD and other osteoporosis therapies in daily clinical practice. This data is unique as it includes elderly patients with multiple co-morbidities, of whom a few are likely to meet the criteria to be included in controlled trials. It therefore assists with the interpretation of how findings from randomised controlled trials may translate into routine clinical practice. The longer duration of follow-up and larger study population allow us to more confidently interpret these results. It is promising that many of the findings described in the randomised controlled trial setting still translate to daily clinical care, notably the beneficial effects on spine BMD and vertebral fracture incidence. This may add reassurance to clinicians who are selecting appropriate patients to commence anabolic therapy for severe osteoporosis in daily clinical practice.

In summary, teriparatide is an anabolic agent used in the treatment of severe osteoporosis under restricted following guidance from regulatory authorities. It has demonstrated superiority in improving BMD and reducing fracture risk in multiple patient populations in randomised controlled trials. Here, we report upon observational data recorded over an 11.5-year period in 724 women comparing the outcomes in those treated with TPTD versus those treated with standard care. Those treated with TPTD in routine clinical practice have an improved spinal BMD and a reduced incidence of vertebral fractures. Our study therefore suggests that TPTD may be preferable to standard therapy in women with severe spinal osteoporosis.

Fig. 1 Gains in Bone Mineral Density (BMD) shown in the Spine (panel A) or in the Total Hip and Femoral Neck (panel B) measured over the course of the study. Values are mean ± standard error. * indicates *p* values less than 0.01 referring to difference between groups by t test. Change in BMD refers to total change in BMD from baseline scan at study entry to repeat scan date. There was no significant difference in the scan interval between groups. Within the Teriparatide (TPTD) cohort, BMD information was available in 224 women (year 1), 227 women (year 2) and 49 women (year 5). Within the standard care (SC) group, BMD information was available in 59 women (year 1), 49 women (year 2) and 26 women (year5)

Table 5 Fracture incidence in the study population

	TPTD ($n=496$)	Control ($n=228$)	Unadjusted p value	Adjusted total FRAX	Adjusted hip FRAX	Adjusted propensity Score
Duration of follow-up (months)	53.8	54.4	0.86	0.97	0.97	0.98
Vertebral fractures	24 (4.8%)	23 (10.1%)	0.01	0.01	0.01	0.03
Non vertebral fractures	105 (21.2%)	49 (21.5%)	0.92	0.81	0.64	0.53
Multiple vertebral fractures[a]	9 (1.8%)	9 (3.9%)	0.09	0.12	0.13	0.35
Multiple non vertebral fractures[a]	23 (4.7%)	6 (2.6%)	0.19	0.11	0.10	0.06

Values are numbers (percentage), unadjusted p values refer to difference in groups by Chi square test, adjusted p values refer to significance attributable to teriparatide as a categorical predictor of outcome in regression models incorporating FRAX total fracture score or FRAX hip fracture score, or propensity scores, respectively

[a]Defined as two or more

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This was a retrospective audit of normal clinical care. Following discussion with NHS Lothian Research Office, it was agreed that formal ethical approval was not required.

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