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Longitudinal audit of outcomes subsequent to teriparatide therapy

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Abstract

Aims

The aim of this study was to determine the outcomes of patients with 7 year follow-up from starting teriparatide in a real world setting.

Methods

A retrospective chart review was conducted on patients who received teriparatide therapy from 1/1/2011 to 1/9/2014. 114 patients were included. Demographics, diagnosis of osteoporosis, management of osteoporosis before and after teriparatide and outcomes after teriparatide including new fracture and mortality were examined.

Results

There were 93 women (82%) and 21 men, median age 74 years. 103(91%) patients had a vertebral fracture before commencing teriparatide. 62(63%) patients received anti-resorptive agents before teriparatide. 47(42%) patients had a new clinical fracture within seven years of starting teriparatide(n=112). Median time to fracture from teriparatide initiation was 48 months(IQR 24-63). 27(58%) of these were non-vertebral fractures. 7% had a new clinical vertebral fracture within 36 months of starting teriparatide. 12(14%) patients were not on anti-resorptive treatment after finishing teriparatide.

Discussion

This is the first study to provide 7-year patient outcomes after starting teriparatide. The incidence of non-vertebral fractures after teriparatide was higher compared to large observational studies. Careful selection of patients for teriparatide therapy is essential in clinical practice.

Introduction

Osteoporosis is the commonest bone disease worldwide[1] and is associated with high morbidity, mortality and socio-economic costs[2]. Most osteoporotic fractures occur in older women[3]. It is estimated that 22 million women and 5.5 million men in the EU had osteoporosis in 2010, affecting 6% of men and 21% of women aged 50-84 years[4]. This is due to rise to 33.9 million in 2025, corresponding to an increase of 23%[5].

Vertebral fractures, fractures of the forearm, hip fractures and proximal humerus fractures are the most common osteoporotic fractures[6]. Prevalent vertebral fractures predict future vertebral and nonvertebral fractures, and are associated with a 5-fold increased risk of sustaining a further vertebral deformity[7]. The risk increases dramatically with both number and severity of the prevalent vertebral fractures[7]. Only one third of vertebral fractures found on radiographs come to medical attention[8].

Teriparatide and other anabolic agents have been used less often than the less expensive and more convenient anti-remodelling drugs[9]. Teriparatide is recommended for up to two years in patients with osteoporosis at very high risk of fracture, such as those with severe or multiple vertebral fractures[10]. Rebound loss in bone mineral density (BMD) is well identified in this cohort after completing treatment[11,12], therefore treatment with an anti-resorptive agent after teriparatide is essential[10].

Anti-resorptive agents such as bisphosphonates and denosumab have proven efficacy in fracture risk reduction in osteoporosis. The Fracture Intervention Trial (FIT) demonstrated that alendronate therapy reduces the frequency of morphometric and clinical vertebral fractures, as well as other fractures[13,14]. The phase 3 FREEDOM trial demonstrated that denosumab is an effective and safe treatment for osteoporosis in post-menopausal women, reducing the risk of both vertebral and non-vertebral fractures related to osteoporosis[15]. Denosumab is also effective in reducing both hip and vertebral fracture risk in high risk subgroups[16].

The aim of this study was to determine the outcomes of patients with seven years of follow-up after finishing teriparatide therapy.

Methods

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. A retrospective chart review was conducted from January 2021 to March 2021. Cases included in the study were identified using records of teriparatide nurse training . All patients that received teriparatide therapy from 1/1/2011 to 1/9/2014 were included. This allowed for a seven year follow-up interval after starting teriparatide therapy to assess patient outcomes. Data was collected and analysed using Microsoft Excel. Variables examined include demographic characteristics of the patients at baseline, diagnosis of osteoporosis prior to commencing teriparatide therapy, the management of osteoporosis before and after teriparatide therapy including early cessation of therapy, and patient outcomes for seven years after starting teriparatide including new fractures and mortality. DXA scanning did not include morphometry. Percentages presented for each variable are of the subgroup of participants that had data available rather than the whole group.

Results

Demographic and clinical characteristics

114 patients were included in the study. Demographic and clinical characteristics of the patients where available are summarised in *Table 1*.

	No of cases	**Percentage (%)**
Gender (n=114)		
Male	21	18
Female	93	82
Age (n=114)		
30-39	1	
40-49	2	
50-59	8	
60-69	24	
70-79	51	
80+	28	
BMI (n=48)		
18.5 or less	2	4
18.5- 24.99	19	40
25.0-29.99	21	44
30+	6	12
Smoking (n=67)		
Yes	35	52
No	32	48
History of long term steroid therapy (n=92)		
Yes	20	22
No	72	78
Vitamin D status (n=54)		
Deficiency (<30nmol/L)	6	11
Insufficiency (30-50nmol/L)	16	30
Optimal (>50nmol/L)	32	59
Number of pre-existing co-morbidities (n=107)		
0	9	8
1	14	13
2	14	13
3	21	20

4	22	21
5	14	13
6	13	12
Pre-existing co-morbidities (n=107)	31	
Hypertension	14	
Rheumatoid arthritis	13	
Cardiovascular disease	11	
Hypothyroidism	10	
TIA/stroke	7	
Diabetes mellitus	5	
Hyperthyroidism	5	
Chronic Kidney Disease	4	
Coeliac disease	2	
Liver disease		
Treatment before and after teriparatide therapy		
Treatment before teriparatide (n=98)	36	37
No	62	63
Yes	58	94
Oral bisphosphonate	1	1.5
IV bisphosphonate	1	1.5
Denosumab	1	1.5
Strontium	1	1.5
Raloxifene		
Treatment after teriparatide (n=87)	59	68
Anti-resorptive agent	12	14
Not on anti-resorptive agent	1	
Other agent: strontium	10	
Ca/Vit supplements only	1	
No therapy	16	18
Died during teriparatide treatment		

Table 1: Demographic and clinical characteristics of patients started on teriparatide therapy

There were 93 women (82%) and 21 men (18%). The median age at start of teriparatide therapy was 74 years (IQR= 67-79). Data on pre-existing co-morbidities were available for 107 of the

patients in the study (*Table 1).* Nine (8%) patients had no pre-existing co-morbidity before commencing teriparatide therapy. Fourteen (13%) patients had one pre-existing co-morbidity. Eighty-four (79%) patients had two or more pre-existing comorbidities before commencing teriparatide therapy.

Diagnosis of osteoporosis

Seventy-eight (68%) patients had a DXA scan performed before starting teriparatide therapy. Results were available for 68 of these patients. Thirty-six (32%) patients did not have a DXA scan before starting teriparatide therapy, and were treated based on the X-ray findings. Of the 68 cases with available DXA results, 42 (60%) patients had a DXA diagnosis of osteoporosis, 23 (35%) had osteopenia and three (5%) had a normal BMD (bone mineral density).

Of the 23 patients with a diagnosis of osteopenia on DXA, 10 (43%) patients had a single vertebral fracture and 9 (39%) had multiple vertebral fractures. One DXA-defined osteopenic patient had a history of non-vertebral fractures (multiple pelvic insufficiency fractures) and two patients had a history of both multiple vertebral fractures and a non-vertebral fracture. One patient had an initial diagnosis of single vertebral fracture made on LVA on DXA, later out-ruled by MRI imaging. Of the three participants with normal BMD on DXA before starting teriparatide, one had sacral ala fractures; the other two participants with normal BMD on DXA had three vertebral fractures.

Table 2 shows the diagnosis of fractures by plain film X-ray before commencing teriparatide (n=113). One hundred and three (91%) patients had a vertebral fracture diagnosed by plain film X-ray before starting teriparatide therapy.

Fracture diagnosis by X-ray (n=113)	**No. of cases**
Vertebral fracture	103 (91%)
Single vertebral fracture	*44*
Multiple vertebral fracture	*59*
Vertebral fracture with previous history of fracture at non-vertebral site	18
Non-vertebral fracture only	8
No fracture	2

Table 2: Fracture diagnosis on X-ray in patients that received teriparatide therapy (n=113)

Treatment characteristics

Treatment of osteoporosis before teriparatide therapy

Treatment of osteoporosis before starting teriparatide therapy is summarised in *Table 1* (n=98). Thirty-six (37%) participants were naïve to anti-resorptive agents before starting teriparatide. Sixty-two (63%) participants had received previous treatment for osteoporosis before starting teriparatide. Fifty-eight of these had received an oral bisphosphonate.

Treatment of osteoporosis after teriparatide therapy

No record of therapy after teriparatide was available in 27 of the 114 cases in the study (23%). Fifty-nine (68%) participants took an anti-resorptive agent after teriparatide (n=87) (*Table 1*). Twelve (14%) participants were not on anti-resorptive therapy after finishing teriparatide therapy.

Early cessation of therapy

Thirty-four (30%) of the 114 participants included in this study did not complete the full 18-24 month course of teriparatide therapy. Sixteen (14%) patients died during the course of teriparatide therapy. Eighteen (16%) stopped teriparatide therapy early; six in the first three months of therapy, five between three and twelve months and seven after one year of therapy. Reasons for early cessation of therapy in this group included difficulty performing/tolerating injections, cessation by physician as a precaution due to new symptoms, prescription not refilled by patient and patient preference to switch back to bisphosphonate therapy.

Outcomes

Mortality

Fifty-three (46%) participants that received teriparatide therapy have died (n=114). Forty-three died within seven years of starting teriparatide: 16 during teriparatide therapy and 27 within five years of finishing teriparatide therapy. The median age of the 16 patients that died during teriparatide therapy was 79 years. All patients in this group had pre-existing vertebral fractures. All patients in this group also had two or more pre-existing co-morbidities, with 11 participants having 4 or more pre-existing co-morbidities. Three of the participants in this group had a new fracture during teriparatide therapy.

Fractures

65 (58%) participants had no new fracture during or after teriparatide therapy (n=112). Thirteen of these participants died during the course of teriparatide, accounting for 12% of the total study participants. 47 (42%) participants had a new fracture during or after receiving teriparatide therapy (n=112). Time to fracture for these 47 patients is outlined in *Table 3*. Median time to fracture from when teriparatide was started was 48 months (IQR=24-63). Thirteen patients had a new fracture

diagnosed during teriparatide therapy, three of which also died during the course of the teriparatide therapy. There was no significant age difference between those who had a fracture and those that did not, allowing for deaths (median age of 73 (IQR= 67-70, n=28) in those with fracture *versus* median age of 71 (IQR= 61-76)(n=34) in those with no fracture).

Time to fracture after starting teriparatide therapy (n=47)	**Vertebral**	**Non-vertebral**	**Total (vertebral and non-vertebral)**
0-24 months	3* (3%)	11* (10%)	13 (12%)
0-6 months	1(1%)	*2 (2%)*	3 (3%)
7-12 months	0	*5 (5%)*	5 (5%)
13-18 months	0	*0*	0
19-24 months	2 (2%)	*4 (4%)*	6 (5%)
25-36 months	5 (4%)	5 (4%)	10 (9%)
37-48 months	2 (2%)	3 (3%)	5 (4%)
49-60 months	5 (4%)**	5 (4%)**	7 (6%)**
61+ months	6 (5%)***	7 (6%)***	12 (11%)***

Table 3. Time to fracture during teriparatide therapy and during 6 month intervals for follow-up period. (*one case had both vertebral and non-vertebral fracture, ** 3 cases had both a vertebral and non-vertebral, *** one case had both vertebral and non-vertebral fracture)

Table 4 classifies the fractures diagnosed during or after teriparatide therapy (n=47). 17 (36%) patients were diagnosed with a vertebral fracture. 27 (58%) patients were diagnosed with non-vertebral fractures. Three patients were diagnosed with both vertebral and non-vertebral fractures.

Fracture type (n=47)	**No. of cases**	**Percentage (%)**
Vertebral fracture(s)	17	36 (15% of 112)
New	*16*	
Progression of existing fracture	*1*	
Non-vertebral fracture	27	58 (24% of 112)
Femur	*12*	
Distal forearm	*11*	
Pelvic	*3*	
Ankle	*1*	
Fibula	*1*	

Both vertebral and non-vertebral fractures	3	6
Femur	*2*	
Distal forearm	*1*	

Table 4. Classification of fractures during or after teriparatide therapy

Data on the duration of teriparatide therapy and treatment after teriparatide was available for 37 of the 47 participants with fractures after starting teriparatide. 27 participants received a full course of teriparatide therapy (18-24 months). 30 participants received anti-resorptive therapy after teriparatide. There was a delay of one year in commencing anti-resorptive therapy in the case of 2 participants. Seven participants did not receive anti-resorptive therapy after teriparatide; five on Ca and Vitamin supplements only and two on Vitamin D supplements only.

Outcomes of participants that did not receive anti-resorptive therapy after teriparatide

Twelve participants did not receive anti-resorptive therapy after teriparatide. Eight received the full 18-24 month course of teriparatide. Seven participants in this group were diagnosed with a new fracture; two during teriparatide therapy, five after stopping teriparatide therapy. Three participants died; one during the first six months of teriparatide therapy and two patients three and four years after finishing teriparatide therapy respectively.

Discussion

This retrospective observational study provides novel data on the use of teriparatide in the "real world" clinical setting and adds to data on outcomes following teriparatide therapy. It is the first study that provides follow-up data for 7 years after starting teriparatide. 58% of participants in our study had no new fracture after teriparatide therapy. Most new fractures after teriparatide were non-vertebral fractures (58%).

Our study represents a population at high risk of fracture. The majority of participants (91%) had one or more vertebral fractures before starting teriparatide. Moreover, almost 60% of participants had multiple vertebral fractures before starting teriparatide.

Fracture incidence after teriparatide was higher in our study compared to the large observational studies of teriparatide therapy in the US and Europe[17,18,19]. Our study had a higher incidence of new vertebral fractures during the 18-month follow-up period compared to European ExFOS (5% in our study *vs* 3.6% in ExFOS). Our study had a higher incidence of non-vertebral (NV) fractures than the DANCE study in the US for both the 24-month treatment period and 24-month follow-up period after finishing teriparatide; 10% *vs* 3.84% for the treatment period, 8% vs 2.14% for the follow-up

period. Incidence of new NV fractures was also higher in our study compared to ExFOS (5% in our study *vs* 3% in 18-month follow-up).

Comparing our study to these large observational studies is limited by differences in both baseline characteristics of the study population and their treatment characteristics before starting teriparatide. Overall our study population demonstrated a higher risk profile for fracture risk recurrence than large observational studies[17,18,19]. For example, 57% of participants in DANCE had a previous fragility fracture before starting teriparatide compared to 98% in our study; 77.3% in ExFOS had a history of previous vertebral fracture(s) compared to 91% in our study. In contrast to these large observational studies, a high proportion of our study participants (63%) had also received anti-resorptive therapy in the form of bisphosphonates before teriparatide, reflecting the differences in clinical practice in Ireland and the United Kingdom compared to the US and the rest of Europe at the time. It is well established that the effectiveness of teriparatide is less for these patients than for those who are naive to treatment with a bone resorption inhibitor[20].
Comparison of our study data with randomised controlled trials including the core registration trials for bisphosphonates and denosumab is questionable and must be interpreted with caution as the characteristics of the patients included in such trials are very different and adherence to treatment is often very high, contrary to what is observed in "real life" observational studies. There was a higher incidence of new clinical fractures in our study after 36 months of teriparatide than in both the placebo and alendronate groups in the Fracture Intervention Trial (7.24% in our study vs 2.3% in alendronate group, 5% in placebo group)[13]. Our study demonstrated a similar incidence of new vertebral fracture at 36 months compared to post-hoc analysis of higher risk subjects taking denosumab in the FREEDOM trial (7% in our study vs 7.52% in FREEDOM)[15].

Our study has limitations. It is a retrospective observational study resulting in missing data. Clinical fractures were diagnosed on the basis of patients presenting with symptoms of a fracture (e.g. back pain) and imaging to screen for new fractures was not performed.
Comparing fracture incidence with other studies is limited given the difference in study design, the heterogeneity of the study participants across different studies as well as the small study size and lack of a control group in our study to allow for risk ratio calculations. Denosumab was largely unavailable during the study period. It has since become readily available, thus adherence with anti-resorptive treatment after teriparatide is now more achievable.

In conclusion, this is the first study to provide 7-year patient outcomes after starting teriparatide, 4 years longer than previously published. This was a high risk population with a high burden of vertebral fractures. Most new fractures after teriparatide were non-vertebral. The incidence of non-vertebral fractures after teriparatide was higher compared to large observational studies in both Europe and the US. Careful selection of suitable candidates for anabolic therapy is paramount in clinical practice.

Declaration of Conflicts of Interest:
None declared.

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