Teriparatide (Forsteo®) for the treatment of bisphosphonate-induced atypical fractures

Lead author:
Hayley Johnson
Regional Drug & Therapeutics Centre (Newcastle)
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Summary

- Teriparatide (Forsteo®, Eli Lilly) is a synthetic polypeptide consisting of the 1-34 amino acid N-terminal region of human parathyroid hormone. Teriparatide is not licensed for the treatment of bisphosphonate-induced atypical fractures, and it is not currently under regulatory review for this indication.

- Atypical fractures tend to occur lower down in the subtrochanteric and femoral shaft regions due to low or no impact trauma. They are often associated with a prodrome period of thigh pain, circumferential cortical thickening, and cortical stress lesions and may heal poorly. Estimates of incidence vary but one study suggests 55 incidences per 100,000 person years. There are no clear guidelines for the treatment of atypical fractures caused by bisphosphonates. The place in therapy for teriparatide remains unknown.

- There is little published evidence for the efficacy of teriparatide in atypical fractures. The majority of evidence is in the form of case reports, and no robust randomised controlled trials have been performed. Concurrent pharmacological or surgical treatments, reported outcomes, time to teriparatide initiation, and treatment duration varied between reports.

- Overall, the results of published case reports and other small studies appear positive but are difficult to interpret. The optimal regimen and precise place in therapy of teriparatide remain uncertain.

- There is no specific safety data on the use of teriparatide in the treatment of bisphosphonate-induced atypical fracture, though those affected will likely closely match the licensed population, for which safety is established. The most commonly reported adverse effects are nausea, limb pain, headache and dizziness. There are concerns that long term use of teriparatide may be associated with an increased risk of osteosarcoma. Treatment should therefore be limited to a maximum of 24 months.

- Teriparatide is a high-cost PbR-excluded drug. One maximum length course of 20 micrograms per day for two years costs £6,525.12 per patient. Patients need to be suitably trained in order to self-administer it. Comparisons with existing treatments are difficult as there is no definitive standard therapy.

- Using a rough estimation, there are approximately six atypical fractures caused by bisphosphonates in the NTAG region per year. Treating these fractures with teriparatide would equate to £39,150.72, spread over two years. The concurrent need for surgical intervention and other pharmacological treatments remains unknown.
Introduction and background

Osteoporosis affects more than three million people in the UK, and osteoporotic fragility fractures account for 300,000 hospital presentations annually.\(^1,2\) It becomes more likely with advancing age in both men and women, though post menopausal women experience a dramatic increase in risk. Prevalence increases from 2% in women 50 years of age to 25% at 80 years. More than one in three women and one in five men will sustain one or more osteoporotic fractures in their lifetime.\(^2\)

Bisphosphonates are recommended as the first line treatment for primary prevention of osteoporotic fractures in men and women over 50 years of age with a high risk, and in patients over 70 years of age who are taking large doses of oral corticosteroids. They are also considered first line for secondary prevention in postmenopausal women who have had a previous fragility fracture.\(^3,4\)

Since 2005, the possible association between bisphosphonates and atypical fractures has been discussed in the medical literature. Whilst clear, robust causality has not yet been established, several regulatory authorities worldwide have issued safety advice regarding the risk of atypical fractures with long term bisphosphonate treatment.\(^5\) In the UK, the MHRA published a Drug Safety Update in 2011 reporting the findings of a European review. Recommendations included:

- Checking the contra-lateral femur in patients who present with a femoral shaft fracture, as atypical femoral fractures are often bilateral.
- Considering discontinuing bisphosphonate therapy in those with a suspected atypical femoral fracture.
- Counselling patients to report any thigh, hip, or groin pain that they experience during bisphosphonate treatment.
- Periodically reviewing the need for continued treatment, particularly after five or more years of use. The optimal duration of bisphosphonate treatment for osteoporosis has not yet been established.\(^6\)

Femoral fractures are common in the general population. In adolescents and young adults, fractures more commonly occur towards the lower, stronger end of the bone as a result of violent traumatic injuries. In elderly patients, however, femoral fractures tend to occur more commonly in the weaker bone region towards the femoral neck. In contrast, atypical fractures tend to occur lower down in the subtrochanteric and femoral shaft regions due to low impact trauma or even in the absence of any trauma.\(^5,7\)

Atypical fractures are often associated with a prodrome period of thigh pain, circumferential cortical thickening, and cortical stress lesions. A complete transverse or oblique fracture subsequently develops.\(^5,8\) Atypical femoral fractures can have a large impact on quality of life and have been associated with poor healing, possibly due to the prolonged presence of bisphosphonates even when discontinued.\(^6,8\)
Bisphosphonates act by inducing osteoclast apoptosis, which serves to reduce bone resorption. This in turn leads to a reduced rate of bone turnover which slows further loss of bone density. Whilst the precise mechanism as to how bisphosphonates cause atypical fractures is unknown, several studies suggest that a reduced rate of bone turnover leads to increased bone mineralisation. Bone remodelling, which would usually repair any micro-cracks that develop due to normal stressors, is suppressed. The bone becomes more brittle and less able to repair minor damage, leading to gradual propagation of micro-cracks into complete fractures.

The exact incidence of atypical fractures remains unknown. One estimate suggests that they may affect up to 5 in 10,000 people taking bisphosphonates, whilst a Swedish study found an incidence of 55 per 100,000 person years. A recent meta-analysis found an adjusted odds ratio of 1.99 (95%CI 1.28-3.10, p=0.01).

There are no clear guidelines on the treatment of atypical fractures. Whether patients, especially those with incomplete fractures or no pain, should be treated conservatively or surgically remains controversial. Treatment strategies include discontinuation of the bisphosphonate and/or switching to a different osteoporosis treatment, avoiding weight bearing, pharmacological approaches, and surgical interventions. Other antiresorptives such as denosumab should be discontinued. Strontium may be used alone or in combination with teriparatide, though safety concerns mean it is often unsuitable for patients most at risk of atypical fractures. One US guideline discusses the role and ambiguous evidence base for teriparatide and other medical interventions, but makes no clear recommendations on their use.

Teriparatide (Forsteo®, Eli Lilly) is a synthetic polypeptide consisting of the 1-34 amino acid N-terminal region of human parathyroid hormone (HPH). HPH primarily maintains calcium homeostasis through actions on renal calcium retention, producing 1,25-dihydroxyvitamin D, and through its anabolic effects on bone. The 1-34 portion appears to be responsible for most of the hormone’s biological activity. It is licensed for the treatment of osteoporosis in men and postmenopausal women at increased risk of fracture, as well as osteoporosis caused by glucocorticoid therapy. It is administered once daily by subcutaneous injection for a maximum of 24 months. NICE recommends teriparatide as an option for the secondary prevention of osteoporotic fractures in post menopausal women who can’t take bisphosphonates or strontium ranelate. It also recommends teriparatide as an alternative treatment in women who have fractures along with falling bone density when taking alendronate, risedronate, or etidronate for one year. The aim of using teriparatide is to optimise recovery of atypical fracture, minimise risk of contra-lateral fracture, and other fragility fractures.

This document will narratively review the rationale and evidence for the efficacy of teriparatide in treating bisphosphonate-induced fractures caused by bisphosphonates.
Clinical evidence

No large, robust controlled trials have been performed, and consequently no meta-analyses are available. Clinical use is therefore primarily guided by prior plausibility, expert opinion, and case reports. The available evidence is generally unreliable and firm conclusions cannot be drawn.

A systematic review by Zhang et al investigated the role of teriparatide in healing fractures.\(^{16}\) It is not limited to bisphosphonate-related atypical healing. Due to the paucity of trial data, the review relied on published case reports or case series, meaning the applicability of the review to clinical practice is ambiguous. The authors concluded that despite the lack of prospective trials, teriparatide is a viable treatment option based on its pharmacology and apparent success in case reports.

One prospective study has been published by Chiang et al.\(^{17}\) It included 14 patients (13 females and one male, age 76 ±1.9), who presented with thigh pain and who had been taking bisphosphonates for four to ten years. Six patients had a complete fracture and eight had incomplete fractures. Five were treated with teriparatide whilst the others were managed conservatively. Patients were not randomised, and the two groups were not evenly matched. Details of conservative management are not adequately reported. Of the five treated patients, two achieved fracture union, two were described as pain-free and three experienced an improvement in pain. Markers of increased bone remodelling were present in all five patients. Of the nine patients managed conservatively, three went on to receive surgery. One patient achieved fracture union and became pain-free, whilst the others had non-unions and ongoing pain. The serious methodological flaws in this study limit the ability to draw clear conclusions from its results.

Published case reports present a similar picture.\(^{18,19,20,21}\) All cases include post-menopausal women. Some patients received surgical interventions and/or strontium ranelate. Time from fracture to treatment initiation varied considerably. Differences in reported treatments and outcome measures preclude pooling of results or production of robust conclusions. Case reports tended to report on treatment initiated months after the fracture occurred. In clinical trials, treatments are usually initiated within one week of fracture. Given the aetiology of atypical fractures, a delayed presentation is more likely to reflect clinical practice than earlier initiation used in clinical trials.

One randomized, placebo controlled trial is currently recruiting, with an estimated completion date of December 2019.\(^{22}\)
Safety

Teriparatide has been available as a licensed medicine in the UK since 2007 and its overall safety and tolerability has been well described. The safety profile of teriparatide when used as treatment for atypical fractures has not been established, though this population is likely to closely match the licensed population. The safety of teriparatide in patients less than 18 years of age has not been established. 23

In clinical trials, 82.8% of patients treated with teriparatide experienced adverse reactions compared to 84.5% of placebo treated patients. 23 The most commonly reported adverse effects are nausea, limb pain, headache and dizziness. Orthostatic hypotension commonly occurs following administration of the first few doses and can be effectively managed by placing the patient in a reclining position. Injection site reactions such as erythema and itching can occur with subcutaneous administration. Muscle spasms are common, sometimes occurring soon after the first dose. On very rare occurrences, these can take the form of serious back spasms. Allergic events, including anaphylaxis, are rare and can occur soon after injection. 23, 24, 25

Teriparatide can cause renal impairment and as such is contra-indicated in patients with severe renal impairment and cautioned in moderate impairment. Patients with active or recent renal calculi should use teriparatide with caution as it can cause hyperuricaemia in about 3% of patients. 24, 25

Transient increases in serum calcium can occur in normocalcaemic patients. Changes tend to be slight and return to baseline within 16 to 24 hours. Blood monitoring should be avoided until 16 hours after the most recent dose. Increases in blood cholesterol levels are common, and patients should be regularly monitored. 23, 24

In animal studies, long term administration of teriparatide has been associated with an increased risk of osteosarcoma. Rare reports have emerged following use in humans. Duration of treatment is therefore limited to 24 months in total. Courses should not be repeated within a patient’s lifetime. Patients at increased risk of osteosarcoma, such as those with a history of skeletal metastases, previous skeletal radiotherapy, metabolic bone diseases, hyperparathyroidism, or unexplained elevations of serum alkaline phosphatise should not use teriparatide. 23, 24
Cost analysis

No published economic analyses on the use of teriparatide in the treatment of bisphosphonate-induced atypical fractures were identified.

Teriparatide is available as a pre-filled pen for subcutaneous injection. Patients should be suitably trained in proper injection techniques. It does not require that full resuscitation facilities are available for each injection, and can be safely administered by the patient themselves.

Teriparatide is a high-cost PbR-excluded drug. Teriparatide 250 microgram/mL solution for injection costs £271.88 per 2.4 mL pen (excluding VAT; eMIMS April 2015). Each pen contains 30 doses, but is stable for only 28 days once opened. It must be stored in a refrigerator at all times.

The licensed dose is 20 micrograms daily for up to two years. This dose is used in the majority of available evidence for atypical fractures, though the course duration varies widely. Assuming a maximum duration of 24 months, the cost for one course would be £6,525.12 per patient (excluding VAT). This does not include the cost of injection technique training, or monitoring.

Comparing the potential costs of teriparatide with other treatments is difficult. Since there is no consensus on the best course of treatment for atypical fractures, nor any definitive guidelines on when teriparatide therapy should be initiated, it is unclear whether costs would be additive to existing costs such as surgery.

Accurately estimating the number of patients eligible for treatment is difficult as robust incidence estimates of bisphosphonate-induced atypical fractures are not available. Incidence is dependent on the length of bisphosphonate treatment. One Swedish cohort study estimates 55 atypical fractures per 100,000 person-years.11 (Donnelly)

The prevalence of osteoporosis in the NTAG area is roughly estimated as 2.34%, which equates to 84,909 patients in total. 26,27 NICE estimate that 15% of patients with osteoporosis take medicines, and that 95% of those medicines are bisphosphonates. This would mean that roughly 10,790 people in the NTAG region are taking bisphosphonates for osteoporosis. Given the Swedish incidence rates described above, six atypical fractures could be expected annually in the NTAG region. Treating these fractures with teriparatide would equate to £39,150.72 in drug costs alone. It is worth noting that these figures exclude men with osteoporosis, therefore they are likely underestimates.
Points to consider

Teriparatide is not licensed for the treatment of bisphosphonate-induced atypical fractures. There are no clear guidelines or consensus on how atypical fractures should be managed. The majority of evidence for the efficacy of teriparatide is derived from case reports. No good quality randomised controlled trials have been performed. Concurrent pharmacological or surgical treatments, reported outcomes, time to teriparatide initiation, and treatment duration varied between reports. Overall, the results of published case reports appear positive but are difficult to interpret. The optimal regimen and precise place in therapy of teriparatide remain uncertain.

There are no specific safety data on the use of teriparatide in the treatment of bisphosphonate-induced atypical fracture, though those affected will likely closely match the licensed population, for which safety is established. The most commonly reported adverse effects are nausea, limb pain, headache and dizziness. There are concerns that long term use of teriparatide may be associated with an increased risk of osteosarcoma. Treatment should therefore be limited to a maximum of 24 months.

Teriparatide is costly, with one two year course of 20 micrograms per day costing £6,525.12 per patient. Patients need to be suitably trained in order to self-administer it. No special facilities are required for administration. Comparisons with existing treatments are difficult as there is no definitive standard therapy. Using a rough estimation, there are approximately six atypical fractures caused by teriparatide in the NTAG region per year. Treating these fractures with teriparatide would equate to £39,150.72. The need for concurrent surgical intervention and other pharmacological treatments remains unknown.

Author’s declaration: The author has no relevant interests to declare.

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