CASE REPORT

Management of atypical femoral fracture in a patient with osteogenesis imperfecta

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SUMMARY

Osteogenesis imperfecta (OI) is a generalised connective tissue disorder associated with low bone mass, bone fragility and increased susceptibility to fractures. First-line treatment to improve bone mineral density (BMD) is usually with bisphosphonates but long-term usage has been associated with uncommon complications such as atypical femoral fractures (AFF). Treatment with teriparatide in this situation has been reported with positive outcomes. However, choice of treatment after 2 years of teriparatide has not been well studied or reported. We describe a patient with OI treated with bisphosphonates for 9 years, who then suffered a spontaneous AFF, was subsequently started on teriparatide for 2 years followed by 6 monthly Denosumab. 1 year post-treatment with Denosumab, there was significant improvement in BMD, good fracture healing and no new fractures. This case highlights the potential use of denosumab following 2 years of teriparatide treatment in patients with OI with AFF.

BACKGROUND

Osteogenesis imperfecta (OI) is a group of inherited connective tissue disorders with wide phenotypic and molecular heterogeneity. The majority are attributed to autosomal-dominant mutations in genes encoding for type I collagen (COL1A1 and COL1A2). These mutations subsequently result in various defective molecular processes, including defective collagen synthesis, defective collagen processing, such as post-translational modification and cross-linking, and altered structural integrity of collagen. Type I collagen is largely involved in the formation of the extracellular matrix in bones, these mutations thus cause diminished bone mass, impaired bone mineralisation and bone deformities. Recent studies also report that defects in osteoblast differentiation and function further contribute to decreased bone quality.¹ As a result, the primary concern in patients with OI is their susceptibility to multiple fractures with little or no trauma and variable deformities of long bones. While its primary clinical manifestation involves the skeleton, it is also associated with secondary features such as blue sclerae, dentinogenesis imperfecta, hearing impairment, scoliosis, pulmonary function impairment, cardiac valve abnormalities and ligamentous laxity.² In 2010, the International Nomenclature Group for Constitutional Disorders ICHG of the skeleton (INCDS) grouped the known OI syndromes into five groups, namely (I) non-deforming OI with blue

sclerae blue sclerae, (II) perinatally lethal OI, (III) progressively deforming OI, (IV) common variable OI with normal sclerae and (V) OI with calcification in interosseous membranes.³

The main goals of treatment in OI are to improve bone mineral density (BMD), decrease fracture incidence and maximise mobility. Bisphosphonates and teriparatide have been studied via a randomised, placebo-controlled study and reported to be effective in managing OI.^{4,5} Denosumab on the other hand have only been looked at in case series for adults,⁶ and current prospective trials are in the paediatric population.^{7,8} Currently, bisphosphonates, which are synthetic analogues of inorganic pyrophosphate, are still the most widely used due to its benefits being more extensively studied.⁵ Multiple studies have shown that bisphosphonates decrease bone resorption, increase BMD and reduce fracture risk.^{4,9} However, long-term treatment with bisphosphonates has been shown to be associated with uncommon complications such as atypical femoral fracture (AFF) and osteonecrosis of the jaw.^{10,11} In such situations, case reports have shown the benefits of discontinuing bisphosphonates and starting the patient on teriparatide.^{12,13} Teriparatide is a parathyroid hormone analogue that effectively stimulates bone formation and reduce fracture risk with few adverse effects. It has been studied in patients with type I OI and shown to have beneficial effects.¹⁴ However, its maximum usage is limited to 2 years due to the risk of osteosarcoma reported in rat model. Subsequently, there has been limited studies exploring the pharmacological options after 2 years of treatment with teriparatide. In our case report, we report a patient with OI on bisphosphonate therapy complicated by AFF and subsequently successfully treated with teriparatide and denosumab.

CASE PRESENTATION

A 61-year-old man with OI type IV was referred to us for management of low BMD. A BMD done in 2003 revealed a T score of -3.4 (BMD 0.620 g/cm^2) at the spine and a T score of -3.5 (BMD 0.611 g/cm^2) at the hip and he was started on bisphosphonates therapy for a total duration of 9 years. He was initially on alendronate 70 mg weekly for 2 years, followed by etidronate 400 mg every fortnight from 2005 to 2007 and finally put back on alendronate 70 mg from 2007 to 2012. During this period, he suffered a left neck of femur fracture in 2010 which was managed conservatively. Subsequently, in 2012, he presented to the clinic with complaints

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Figure 1 X-ray of right hip showing right atypical femoral fracture.

of right hip pain. A right hip and pelvic X-ray was done which showed a new spontaneous transverse fracture over the subtrochanteric region of the right proximal femur (figure 1). The clinical and radiographic presentation was consistent with the American Society of Bone and Mineral Research (ASBMR) Task Force 2013 Revised case definition for atypical femoral fracture (AFF).¹⁵ We referred our patient for surgical management, but our patient declined surgery. At that time, our patient was also not keen for further pharmacological treatment and was continued solely on calcium and vitamin D tablets. Two years later, after repeated discussion, and with a worsening BMD, our patient finally decided to resume treatment. While it was not certain if his AFF was due to his underlying OI or secondary to long-term bisphosphonate therapy, we decided not to resume bisphosphonate therapy and to start our patient on teriparatide injections at 20 µg/day for 2 years followed by 6 monthly subcutaneous denosumab.

OUTCOME AND FOLLOW-UP

A dual-energy X-ray absorptiometry scan was done prior to initiation of teriparatide and showed a lumbar spine BMD of 0.715 g/cm² and T-score of -2.5. BMD of the hip was 0.584 g/cm² and T-score -3.7. After 1 year of treatment with teriparatide, a repeat BMD showed a substantial improvement of 9.8% (+0.070 g/cm²) in BMD in the lumbar spine (BMD 0.785 g/cm² and T-score -1.9) and 15.7% (+0.092 g/cm²) in the hip (BMD 0.676 g/cm² and T-score -3.0), as well as a healing fracture over the subtrochanteric region (figure 2). Two years after teriparatide treatment, a BMD performed showed no further improvement. We decided to start him on denosumab as he was still at high risk of fractures. One year post-treatment with denosumab, there was further improvement in the BMD at the hip (+0.022 g/cm²) where it was most severe. Calcium levels were checked and no hypocalcaemia was noted. A summary of

Figure 2 X-ray of right hip showing healing fracture.

his BMD results is shown in table 1. He is currently well, with no complaints and no further fractures.

DISCUSSION

Bisphosphonates are widely recognised as the mainstay of treatment for improving BMD in patients with OI.^{2 4 5} However, studies in normal patients with osteoporosis has demonstrated that prolonged usage may result in atypical long-bone fracture. On the other hand, in a recent retrospective analysis by Vuorimies *et al* on children with OI, the authors concluded that subtrochanteric femoral fractures were more likely to occur in more severe types of OI, types III and IV.¹⁶ Thus, it is important to bear in mind that in patients with OI where the underlying disease itself is a clear triggering factor for subtrochanteric fractures, it is difficult to ascertain if the occurrence of AFF is due to long-term bisphosphonate therapy or due to the OI itself. In our case, while we are unable to conclude that the AFF in our patient was secondary to long-term bisphosphonate therapy, we decided to follow ASBMR Task Force recommendations for management of AFF which includes discontinuing antiresorptive agents and reconstruction of nail fixation for incomplete fractures (with cortical lucency) associated with pain.¹⁵ However, our patient declined surgery.

Table 2 shows cases reporting AFF in adults with OI after long-term bisphosphonate therapy.^{11–13 17} In three of the four cases, teriparatide was the treatment of choice after discontinuation of bisphosphonates. A randomised controlled trial by Orwoll *et al* looked at the effects of teriparatide on adults with predominantly type I OI and reported that treatment with teriparatide resulted in an increase in hip and spine areal BMD, vertebral volumetric BMD and estimated vertebral strength. Unfortunately, for the more severe type III and IV OI, anabolic therapy was less effective.¹⁴ Recent research in OI has resulted in the diversity of the molecular genetics of OI to be described

Table 1 Summary of BMD results from 2012 when right AFF was suffered

DXA scan	Events that happened	Lumbar spine			Left hip		
		BMD (g/cm ²)	T-score	LSC* (g/cm ²)	BMD (g/cm ²)	T-score	LSC* (g/cm ²)
2012	Spontaneous AFF after 9 years of bisphosphonate therapy	0.724	−2.4		0.611	−3.5	
2014	Started on teriparatide	0.715	−2.5	0.022	0.584	−3.7	0.026
2015		0.785	−1.9	0.025	0.676	−3.0	0.022
2016	Teriparatide discontinued and denosumab started	0.776	−2.0	0.022	0.680	−3.0	0.027
2017		0.776	−2.0	0.025	0.702	−2.8	0.019

*The ISCD (method is used to determine LSC and reported in g/cm²).

AFF, atypical femoral fracture; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; ISCD, International Society for Clinical Densitometry; LSC, least significant change.

in great detail. For example, in the milder form type I OI, it is a result of quantitative mutations such as premature stop codons, splice-site mutations and insertion/deletions of genes that cause non-sense mediated decay of mRNA from COL1A1 allele, resulting in reduced but normal structured collagen. On the other hand, more severe types such as III and IV are a result of qualitative mutations generally due to missense mutations such as glycine substitutions or splice-site mutations which cause abnormal folding and thus structurally defective collagen.⁴ Thus, as concluded by Orwoll *et al*, stimulating remodelling activity with teriparatide is less likely to be effective in OI types with abnormal bone matrix and cellular dysfunction, because the underlying molecular defect in structurally normal collagen production is affected.¹⁴ In our patient, the specific mutation was not known, however as he had declined surgery, we decided to start him on teriparatide. Initiating our patient on teriparatide resulted in significant improvement in BMD (9.8% in lumbar spine BMD and 15.7% in total hip BMD) and fracture healing. We concur with other authors¹² that anabolic therapy is capable of increasing bone formation and bone mass in this subgroup of patients. This is likely due to teriparatide's ability to stimulate cartilage production to induce callus formation and remodelling.^{18–19} Unfortunately, the use of teriparatide is limited to a duration of 2 years as studies in mice models have shown that use beyond this period is associated with increased incidence of

bone neoplasms such as osteosarcoma.²⁰ Subsequently, there has been no consensus as to the use of antiresorptives or receptor activator of nuclear factor κ B ligand (RANKL) inhibitors after stopping teriparatide.

Denosumab is a human monoclonal antibody to RANKL. Inhibition of RANKL reduces osteoclast activity and prevents bone resorption, similar to bisphosphonates. However, RANKL also targets osteoclasts at a more immature stage, preventing maturation and activation and thus demonstrated a greater ability to prevent bone resorption.²¹ Studies evaluating its effect in adults and children with OI showed a significant increase in BMD with no accompanying adverse effects.²² It has also been shown to decrease bone resorption, increase BMD and reduce risk of fractures in postmenopausal women with osteoporosis. In a recent case report, Uehara *et al* looked at the efficacy of denosumab in three female patients with OI and reported that after 24 months there were no fracture or severe side effects such as hypocalcaemia and the mean percentage changes in lumbar BMD and bilateral hip BMD were 14.7% and 15.1%, respectively.⁶ In view of the more significant positive impact on the hip BMD, we started our patient on 6 monthly denosumab injection and noted improvement in total hip BMD after 1 year of treatment. However, we acknowledge that denosumab may not be safer than bisphosphonates following teriparatide in our patient. Numerous case reports have reported cases of AFF following

Table 2 Summary of AFF cases after bisphosphonate therapy in adults with OI

	Ref 11	Ref 17	Ref 12	Ref 13	Our case
Year reported	2012	2013	2014	2015	2017
Age/gender	75/F	64/F	70/F	21/M	61/M
Type of OI	I	IV	I	IV	IV
Type of bisphosphonate started and duration before AFF occurred	Alendronate 3 years	Pamidronate for 3 years, then zoledronic acid for 2 years	Etidronate for 5 years, then alendronate for 3 years, then pamidronate for 1.5 years then zoledronic acid 1 year	Pamidronate for 3 years, then alendronate for 6 years	Alendronate for 2 years, then Etidronate for 2 years then Alendronate for 5 years
Location of AFF	Right femoral shaft fracture	Right femur subtrochanteric fracture Left mid-diaphyseal fracture	Right femoral shaft fracture	Right femur diaphyseal fracture	Right femoral shaft fracture
Was surgical management offered?	Yes, underwent intramedullary nailing	Not reported	Yes, underwent intramedullary nailing	Yes, underwent intramedullary nailing	Yes, patient declined
Teriparatide started and duration	Not reported	Yes, duration not reported	Yes, 2 years	Yes, case reported at 1-year duration of teriparatide	Yes, 2 years
Measurement of teriparatide treatment success	Not reported	Not reported	X-ray: fracture healing noted at 1 month, at 6 months showed solid healing DXA scan: 16.8% improvement in lumbar spine BMD after 2 years	X-ray: showed healing Bone markers: initial peak decrease in P1NP and NTX markers, followed by progressive decrease over 1 year	DXA scan: 9.8% improvement in lumbar spine BMD and 15.7% improvement in total hip BMD
Treatment after teriparatide	Not reported	Not reported	Zoledronic acid 5 mg/year	Not reported	Denosumab

AFF, atypical femoral fracture; BMD, bone mineral density; OI, osteogenesis imperfecta.

long-term usage of denosumab.^{23–27} In a recently concluded FREEDOM trial which assessed the long-term safety and efficacy of 10 years of denosumab treatment in postmenopausal woman with osteoporosis, two cases of AFF were reported.²⁸ Thus, continuing our patient on denosumab still puts him at a risk of recurrent AFF, and in the event of such cases, discontinuation of denosumab should be considered. Clinicians should also be aware that abrupt discontinuation of denosumab can lead to rebound fracture due to severe bone turnover rebound and rapid loss of BMD.^{29–30}

In summary, atypical femoral fractures while uncommon in occurrence are a potential adverse complication for OI patients being treated with bisphosphonates. However, the diagnosis of bisphosphonate-related AFF is difficult to make in patients with OI, due to the underlying disease process. As with other authors, we recommend the use of teriparatide as part of subsequent management. However, while there are no current studies and case reports that report the use of denosumab after 2 years of teriparatide, clinicians can consider this as a potential treatment option.

Learning points

- Bisphosphonates are the first-line treatment for managing patients with osteogenesis imperfecta (OI) to improve bone mineral density (BMD) and reduce fracture risk. However, long-term treatment can be associated with atypical femoral fractures (AFF). In the event of such complications, subsequent use of teriparatide has been reported to accelerate fracture healing and improve BMD.
- The diagnosis of bisphosphonate-related AFF is difficult to make in patients with OI, due to the underlying disease process.
- Denosumab can be considered a potential treatment option following 2 years of treatment with teriparatide for patients with OI with AFF secondary to long-term bisphosphonate therapy.
- If there are plans to start denosumab, it should not be abruptly discontinued; bridging with bisphosphonate should be commenced to reduce the risk of rebound fractures.

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