Bone marker response in chronic diffuse sclerosing osteomyelitis treated with intravenous ibandronate

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Chronic diffuse sclerosing osteomyelitis (CDSO) is a condition of unknown aetiology which causes sclerosis, predominantly in the long bones and mandible of young women. We report the cases of three women treated with the intravenous bisphosphonate ibandronate, a new treatment for the disease, and discuss the relevance of the bone marker changes seen in these patients.

Case one is a 27 year old woman diagnosed with CDSO at age 21, when she presented with severe and intractable pain in the left thigh. An x ray examination and magnetic resonance imaging confirmed diffuse cortical thickening with reduced medullary cavity, and bone biopsy confirmed the diagnosis.

Treatment with oral risedronate caused rapid but temporary improvement. She then received three infusions of 2 mg ibandronate over 3 months, with immediate symptomatic relief.

Case 2 is a 38 year old woman with a 10 year history of pain in the left tibia and femur. She was diagnosed with CDSO after an x ray examination, isotope bone scan, and bone biopsy, and was treated with excision, bone grafting, and external fixation of the left tibia, which provided symptomatic relief for about 2 years.

A return of symptoms prompted intramedullary nailing of the tibia, which gave relief for a further year. Treatment with six infusions of intravenous pamidronate and then oral risedronate led to some decreased activity on isotope bone scan, but only temporary improvement in symptoms. She then received three infusions of ibandronate 1 month apart, at a dose of 2 mg, 3 mg, and 3 mg, with rapid and persistent improvement in symptoms, and changes in bone markers (table 1).

Case 3 is a 21 year old woman with a 10 year history of pain in the left femur and tibia. Sclerotic changes throughout the femur and tibia were seen on x ray examination, and CDSO was confirmed on bone biopsy. Isotope bone scan showed increased uptake in the femur and femoral head, tibia, and talus. Intramedullary nailing of the femur provided relief of pain for about 2 years, but a 6 month course of intravenous pamidronate altered neither pain levels nor isotope bone scan appearance. The patient then received four infusions of 2 mg ibandronate over 4 months. Pain levels gradually improved after the second infusion, which

continued during the third and fourth treatments, and has been sustained for several months. Surgical intervention is planned on the femoral head.

CDSO is a condition of unknown aetiology, characterised by excess bone deposition, and an x ray examination shows diffuse sclerotic opacity with indistinct borders. Definitive diagnosis usually requires bone biopsy. CDSO typically affects young women, and is associated with sclerosis, predominantly in the mandible, and the diaphysis of long bones.^{1 2} It is linked to episodes of intractable pain and occasionally swelling and tenderness, together with chronic discomfort.¹

A wide variety of treatments have been described, including surgery,² antibiotics, corticosteroids, non-steroidal anti-inflammatory drugs, hyperbaric oxygen, and infliximab.^{3 4} More recently, a satisfactory response in CDSO has been described with calcitonin,⁵ intravenous pamidronate,⁶ oral risedronate,⁷ and disodium clodronate.⁸ The trend towards recurrence of pain after a period of months or years appears inevitable.

We have demonstrated satisfactory responses to ibandronate in patients when alternative bisphosphonates have failed, although we do not know how long this improvement will last. The changes in bone markers are also instructive. Although CDSO is thought to be predominantly a disease of bone deposition and osteoblast activity, bisphosphonates act primarily by inducing osteoclast apoptosis,⁹ although they may also have effects on osteoblasts.¹⁰ We have described a general fall in both osteoblast activity (ostase) and osteoclast activity (osteocalcin and serum crosslaps) in all three patients, with much higher initial osteoblast and osteoclast activity in patient 3, who had the least impressive clinical response. Although only three patients are described, these findings suggest that the levels of bone markers vary significantly between patients, perhaps depending on previous treatments or extent of involvement, but that both osteoblast and osteoclast activity tend to fall after ibandronate treatment.

A much larger study is required to investigate definitively the link between bone enzymes, disease activity, and response to treatment, but we believe that intravenous ibandronate represents a possible new treatment in cases of resistant CDSO.

Table 1 Changes in bone markers after treatment with ibandronate

Serum bone marker	Before ibandronate				After ibandronate			
	Alkaline phosphatase (U/l)	Ostase (µg/l)	Osteocalcin (ng/ml)	Crosslaps (pmol/l)	Alkaline phosphatase (U/l)	Ostase (µg/l)	Osteocalcin (ng/ml)	Crosslaps (pmol/l)
Normal range	42–121	8.7–14.3	4.9–30.5	2304	42–121	8.7–14.3	4.9–30.5	2304
Case 1	65	13.8	33.9	3718	61	7.6	15.8	3372
Case 2	44	6.9	8.8	452	26	4.5	4.4	92
Case 3	204	72.9	78.3	5178	122	66.7	63.0	2893

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Ultrasound ability in early diagnosis of stress fracture of metatarsal bone

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A 42 year old woman, with rheumatoid arthritis for 14 years, treated with leflunomide 20 mg/day and prednisolone 5 mg/day, had mechanical pain over the dorsum of the right foot for 3 weeks. She had increased her walking activities a couple of weeks before the pain started. On clinical examination, there was a marked swelling and painful area on the second metatarsal. Plain radiographs were normal.

Sonography of the foot was obtained with a Esaote MP system and a 7.5–13 MHz linear transducer. Only the dorsal aspect of the foot was required in a longitudinal and axial view. A hypoechoic haematoma with periosteal elevation and

cortical break was seen over the second metatarsal, which corresponded to the pain area (figs 1 and 2). Vascularity was showed on power Doppler mode in the periosteal elevation.

Magnetic resonance imaging (MRI) of the foot was performed a week later (figs 3–5). It confirmed the initial diagnosis, showing a soft tissue oedema, callus, and continuity break in the bone.

A plain radiograph, 6 weeks after the first one, showed a callus corresponding exactly to the area of periosteal elevation seen on sonography and MRI.

Plain radiographs may be normal for several weeks before a callus or a fracture line appears in the case of stress fractures. Early diagnosis in this case depends on MRI or bone scan scintigraphy, which are considered to be the “gold standard”.¹ This observation illustrated the diagnostic ability of ultrasound in the early stage of a stress fracture and another use of ultrasound in rheumatology.

Figure 1 An axial ultrasound image of the second metatarsal bone showed distinct cortical thickening with periosteal haematoma and power Doppler signal.

Figure 2 A longitudinal ultrasound image of the second metatarsal bone showed distinct cortical thickening with periosteal haematoma and power Doppler signal.