Childhood Chronic Recurrent Multifocal Osteomyelitis: Pamidronate Therapy Decreases Pain and Improves Vertebral Shape

HELENA GLEESON, ESKO WILTSHIRE, JULIE BRIODY, JILL HALL, JEFF CHAITOW, DAVID SILLENCE, CHRISTOPHER COWELL, and CRAIG MUNNS

ABSTRACT. ***Objective.*** Chronic relapsing multifocal osteomyelitis (CRMO) results in significant morbidity, especially in those with vertebral collapse. Symptomatic benefit with intravenous pamidronate (PAM) has been shown; however, few studies have demonstrated radiological benefit. We describe clinical and radiological data on 7 pediatric cases of CRMO treated with PAM.

Methods. Retrospective chart review on all children with CRMO treated with PAM. Response to PAM was measured by subjective reports and radiology including vertebral morphometry.

Results. Seven patients (1 male) presented with bone pain at a median age of 8 years (range 5–14). Symptoms had been present for a median of 18 months (range 11–51) before PAM therapy. All patients had involvement of multiple nonspinal sites, 5 children had spinal involvement with vertebral fractures, and 5 had joint involvement. Six cases had symptomatic improvement within 6 months of starting PAM, which was sustained during PAM therapy (median 26 mo, range 6–41) and persisted in the 4 cases who had ceased treatment for the duration of followup (27 mo, range 18–51). The least benefit was seen in the 3 cases with synovial joint involvement. The 3 cases with spinal radiological followup showed modeling of vertebral fractures and in one patient improvement in kyphosis. No radiological improvement in nonspinal lesions was seen.

Conclusion. PAM therapy was associated with symptomatic improvement and vertebral modeling in children with CRMO. We suggest that children with bone pain and/or spinal involvement be considered for PAM therapy early after diagnosis. (First Release Mar 15 2008; J Rheumatol 2008; 35:707–12)

Key Indexing Terms:
CHRONIC RELAPSING MULTIFOCAL OSTEOMYELITIS SAPHO SYNDROME
OSTEOMYELITIS BISPHOSPHONATES PAMIDRONATE PEDIATRIC SPINE

Chronic recurrent multifocal osteomyelitis (CRMO) is an idiopathic, aseptic, inflammatory condition of bone, affecting mainly children and adolescents[1]. It is often present as part of the spectrum of conditions encompassed by SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis).

The cardinal feature of CRMO is mild to moderate bone pain. The bone lesions are often multiple and primarily occur in the cleido-spondylo-metaphyseal skeleton. Although self-limiting, CRMO has a median duration of disease activity of 5.6 (range 0.1–19) years[2] and is associated with significant morbidity[3]. The outcome appears poorest in patients with severely reduced bone mass and vertebral involvement[4]. Radiological findings include osteolysis, osteitis, hyperostosis, osteosclerosis, and eventually ankylosis. Histologically the bone shows features of subacute or chronic culture-negative osteomyelitis.

There is no definitive treatment for CRMO. Nonsteroidal antiinflammatory drugs (NSAID) are often the first line of therapy, but provide only limited improvement in bone pain and do not appear to influence disease duration[5]. The use of antibiotics, corticosteroids, immune modulators, antimetabolites, calcitonin, and colchicine, either alone or in combination, has been reported. None appear to be more efficacious than NSAID[5].

Bisphosphonates are powerful inhibitors of osteoclastic bone resorption that also have antiinflammatory and pain-modifying effects[6]. The limited pediatric and adult data[7-11]

From the Institute of Endocrinology and Diabetes, Departments of Nuclear Medicine, Academic Medical Genetics, and Rheumatology, Children's Hospital at Westmead, Sydney, Australia; and Department of Paediatrics, Wellington School of Medicine and Health Sciences, Wellington, New Zealand.

H. Gleeson, MBBS; C. Cowell, MBBS; C. Munns, MBBS, Institute of Endocrinology and Diabetes, Children's Hospital at Westmead; E. Wiltshire, MBBS, Department of Paediatrics, Wellington School of Medicine and Health Sciences; J. Briody, MBioMedEng, Department of Nuclear Medicine, Children's Hospital at Westmead; J. Hall, RN; D. Sillence, MBBS, Department of Academic Medical Genetics, Children's Hospital at Westmead; J. Chaitow, MBBS, Department of Rheumatology, Children's Hospital at Westmead.

Address reprint requests to Dr. C. Munns, Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, NSW, Australia 2145. E-mail: craigm2@chw.edu.au

Accepted for publication Novewmber 14, 2007.

suggest therapy with bisphosphonates leads to symptomatic improvement in CRMO, but radiological data are lacking.

We reviewed 7 pediatric cases with CRMO treated with intravenous pamidronate (PAM) assessing clinical and radiological outcomes.

MATERIALS AND METHODS

A retrospective chart review of all cases (n = 7; 1 male) diagnosed with CRMO and treated with PAM at The Children's Hospital Westmead between 2000 and 2006 was performed. Approval was obtained from the local ethics committee. CRMO was diagnosed on the presence of multifocal bone lesions on bone scan and one of the following criteria: pustulosis (n = 2), culture-negative chronic osteomyelitis on biopsy (n = 2), and indolent/relapsing and remitting clinical course (clinically excluding culture-positive osteomyelitis or malignancy) (n = 3).

PAM therapy was started following failure of symptomatic response to antibiotics, NSAID, and/or corticosteroids. PAM was administered either monthly at a dose of 30 mg/m^2 (n = 2) or second monthly 1.5 mg/kg (n = 5) and continued depending on clinical response. Bone pain in response to PAM was measured by self-report. Side effects of PAM were also recorded.

Biochemistry. Serum calcium, inorganic phosphorus, and serum alkaline phosphatase were analyzed using routine laboratory methodology. Serum osteocalcin and urinary free deoxypyridinoline (DPD) were measured by a solid-phase 2-site chemiluminescent enzyme immunometric assay (Immulite Analyzer, Diagnostics Products Corp., Los Angeles, CA, USA). Urinary creatinine was measured using a kinetic Jaffe assay (Dade Behring ARX analyzer). Urinary DPD/creatinine ratio was calculated.

Bone mineral density (BMD). BMD was determined by dual-energy x-ray absorptiometry (DEXA) using either a Lunar DPX or a Lunar Prodigy instrument (GE Lunar Radiation Corp., Madison, WI, USA). Measurements for the 2 machines were highly correlated (total body > 0.99, spine > 0.98, femoral neck > 0.97). Subjects were positioned, scanned, and analyzed according to standard manufacturer recommendations and data analyzed using either software version 4.7 (DPX) or 8.10 (Prodigy). DEXA values were converted to age and sex-matched Z-scores as described[12]. Total body, posteroanterior lumbar spine, and femoral neck scans were performed, and provided BMD data for the arms, legs, trunk, total body, lumbar spine (L2–L4), and femoral neck.

Nonspinal site radiology. Radiological examinations of nonspinal sites at initiation and completion or near completion of PAM therapy were available for 4 cases and were reviewed.

Lateral spine radiographs. Lateral spine radiographs were available for review at initiation of and completion or near completion of PAM therapy and at last review in 3 of the 5 cases with spinal involvement. In the other 2 cases spinal involvement was not symptomatic, and therefore monitoring with spine radiographs was not clinically indicated. Vertebral morphometry was performed on lateral spine radiographs of affected vertebrae as described by Smith-Bindman, *et al*[13] by measuring posterior height, middle, and anterior vertical heights of each affected vertebra and expressing them as a ratio of the lower length of the vertebra to allow for magnification (e.g., posterior height/lower length = posterior height ratio; Figure 1). The concavity index (middle height ratio/posterior height ratio) was also calculated[14]. The Cobb method was used to quantify the degree of kyphosis[15]. Significant kyphosis was considered to be present at angles > 45°. All measurements were performed by a single observer (HG) using software on MagicWeb, version VA42A (Siemens), which has an accuracy of 0.01 mm and 1 degree. The coefficient of variation for intraobserver comparisons of vertebral heights ranged from 1.7% (anterior height) to 2.6% (middle height) and for the concavity index, 5.3%[14].

Analysis and statistics. Repeat-measure one-way ANOVA with post-hoc analysis was used to determine significant changes in posterior height ratio, middle height ratio, anterior height ratio, and concavity index at the 3 different timepoints. Paired t-test was used to compare biochemical and BMD data at the initiation and completion of PAM therapy. A p value < 0.05 was taken as statistically significant. Data are presented as median (range) unless stated otherwise.

RESULTS

Presentation (Table 1). Seven patients (one male) with a median age at the onset of symptoms of 8 (range 5–14) years were treated with PAM. The median duration of symptoms prior to treatment start was 18 (11–51) months.

All patients had appendicular skeletal involvement with a median of 4 (1–11) sites affected: metaphyses of the femur and/or tibia (n = 5), the pelvis (n = 3), and the clavicle (n = 3). Five patients had vertebral involvement, 3 of whom had more than 4 vertebrae affected. In addition to the radiological changes of CRMO, skeletal features included bone swelling, pathological long bone fractures, vertebral compression fractures, kyphoscoliosis, and chest wall deformity.

Skin manifestations included palmar-plantar pustulosis (n = 3; 43%) and psoriasis (n = 1; 14%).

Pamidronate therapy. PAM was used for a median of 12 (6–41) months. Two patients are still receiving PAM and followup data after completion of PAM were available for 5 patients at 20 (18–51) months.

Symptomatic improvement. Six patients (86%) reported decreased bone pain within 6 months of starting PAM. Two of these continue on PAM therapy. Of the remaining 4 children who had sustained improvement after stopping PAM for a median of 27 (18–51) months, 2 had knee and ankle effusions requiring joint aspiration and intraarticular corticosteroid therapy. As with those who received only limited benefit, the one patient who perceived no pain relief with treatment had synovial joint involvement (elbow and small joints of the feet).

Radiological improvement. Vertebral morphometry was performed on 12 affected vertebrae in 3 cases. There was significant improvement in posterior height ratio, middle height ratio, anterior height ratio, and concavity index from the start to the completion of PAM therapy in all cases with spinal involvement followed radiologically (Figure 1, Figure 2). The anterior height ratio also demonstrated continued improvement from completion of PAM to last review in one case, Patient 1 (Figure 2).

One patient had a significant kyphosis, which improved by 20° with PAM therapy (60° to 40°; Figure 3).

Persistence of nonspinal lesions or the development of new lesions while undergoing treatment was observed in the 4 cases with radiological followup, including 3 with synovitis.

BMD. Reduced bone mass (DEXA BMD Z-score < –1.5) was present in 6 cases at the start of PAM therapy (L2–L4, n = 5; total body, n = 4). Age-matched BMD Z-scores [mean (SD)] improved at all sites in all patients treated with PAM for longer than 6 months, reaching statistical significance at L2–L4 and the femoral neck, as follows: L2–L4, –1.9 (1.0)

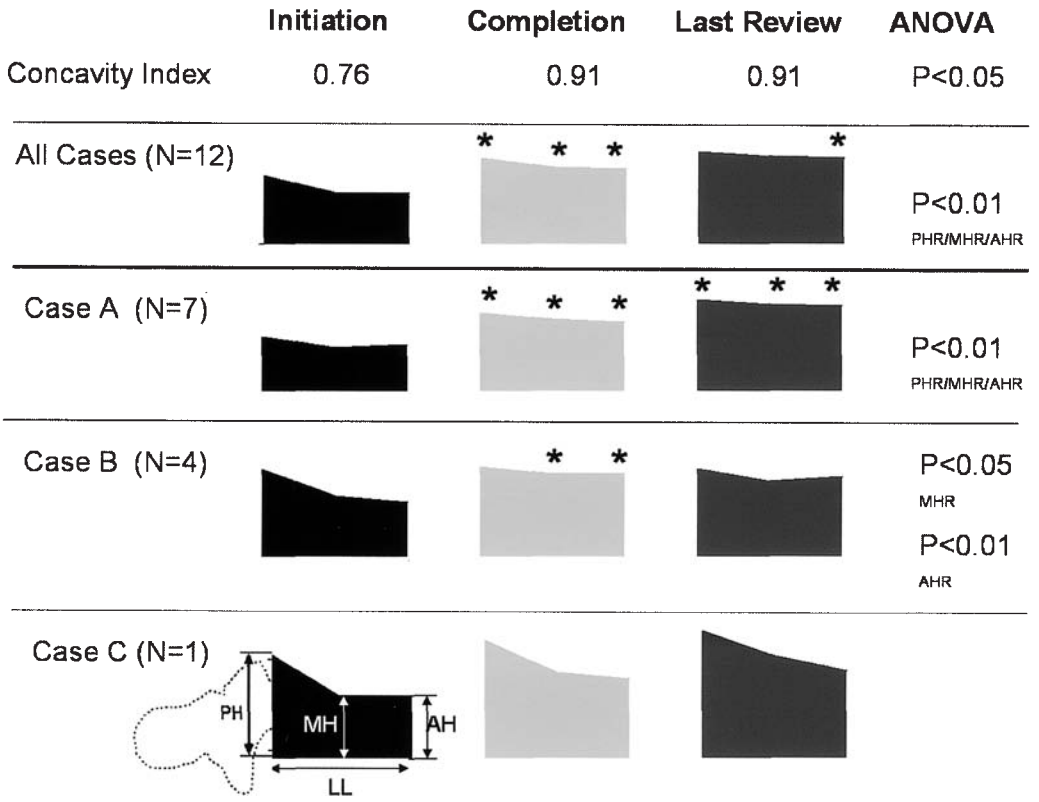

Figure 1. Schematic diagram of vertebra and representation of the changes in vertebral shape including concavity index during pamidronate therapy in the 3 cases with crush fractures, and available radiographs. All cases combined (top row) and each individual case at initiation and completion of PAM and last followup. PH: posterior height, MH: middle height, AH: anterior height, LL: lower length, R: ratio, N: number of vertebra affected. *p < 0.05 compared with previous timepoint on post-hoc ANOVA.

Table 1. Clinical, radiological, and biochemical presentation of the CRMO.

	No. of Patients	Percentage of Total
Musculoskeletal		
Nonspinal bone lesions	7	100
Spinal involvement	5	71
Nonsynovial joint involvement	4	57
Synovial joint involvement	3	43
Reduced bone mass on DEXA (age-matched Z-score ≤ 1.5)	6	86
Extraskeletal		
Skin involvement	4	57
Constitutional symptoms	5	71
Elevated ESR/CRP	3	43

DEXA: dual-energy x-ray absorptiometry; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

vs +0.9 (0.4) (p = 0.008); femoral neck, –2.1 (1.2) vs –0.3 (0.5) (p < 0.05); and total body, –1.2 (1.5) vs +0.1 (0.9) (p = 0.1).

Biochemistry. There were no significant changes in serum calcium, inorganic phosphorus, alkaline phosphatase, osteocalcin, or urinary DPD/creatinine with PAM therapy. Although findings were not significant, in patients who had received PAM for more than 6 months we observed the following: serum alkaline phosphatase decreased by 17% [before vs after PAM: 208.8 (53.1) vs 174.8 (73.7) u/l] and the urinary DPD/creatinine, which before PAM was either above the upper limit or in the upper tertile of the normal range (1.1–26 nM/mM), decreased by 19% [before vs after PAM: 25.4 (12.2) vs 16.6 (12.5) nM/mM], suggesting a reduction in bone turnover.

Side effects of PAM. Four patients had generalized aches and pains and 3 also had fever following their first PAM infusion. One patient developed redness, swelling, and pain at the injection site following an infusion.

DISCUSSION

This report of 7 children with CRMO refractory to NSAID and/or corticosteroids showed that PAM therapy was associated with symptomatic improvement in all patients but one. PAM was also associated with improvement in vertebral shape and a decrease in kyphotic angle. In contrast, the benefit of PAM therapy in nonspinal disease is less clear, with no evidence of radiological improvement in patients with appendicular disease, and synovial joint involvement appearing unresponsive to treatment.

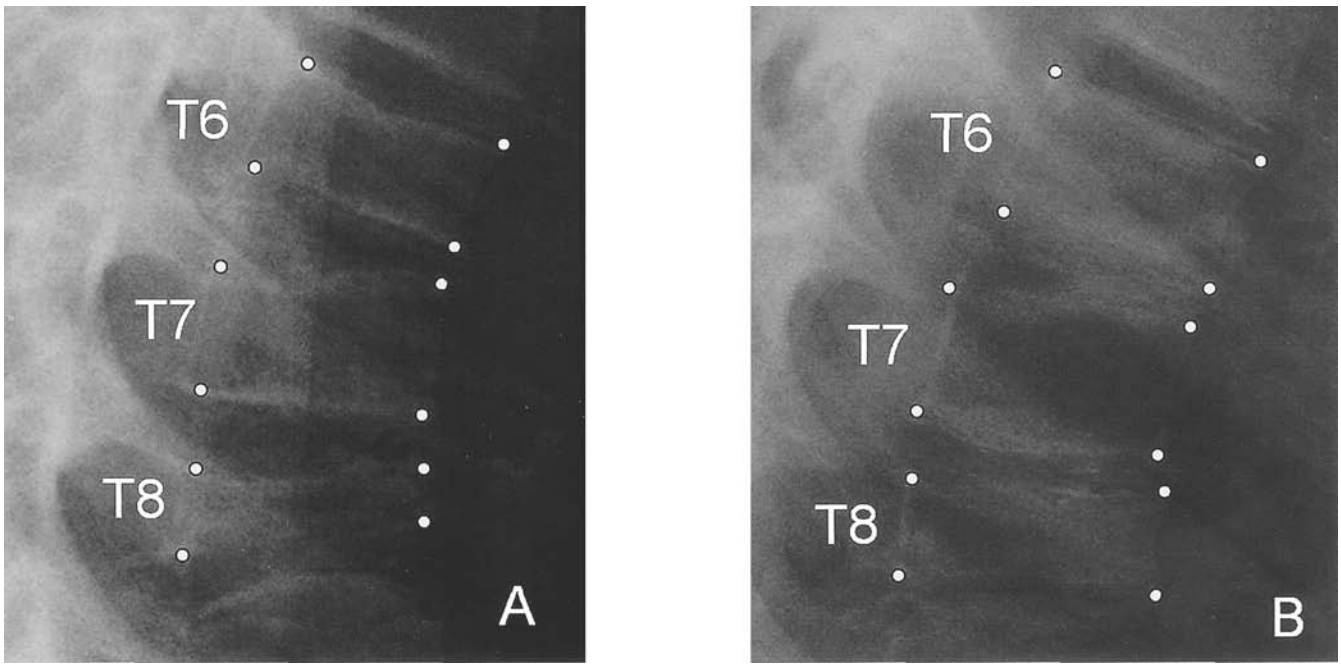

Figure 2. Lateral spinal radiographs of T6–T8 in Patient 1 show improvement in vertebral morphometry from start of pamidronate therapy (A) and at last followup 3 years later (B).

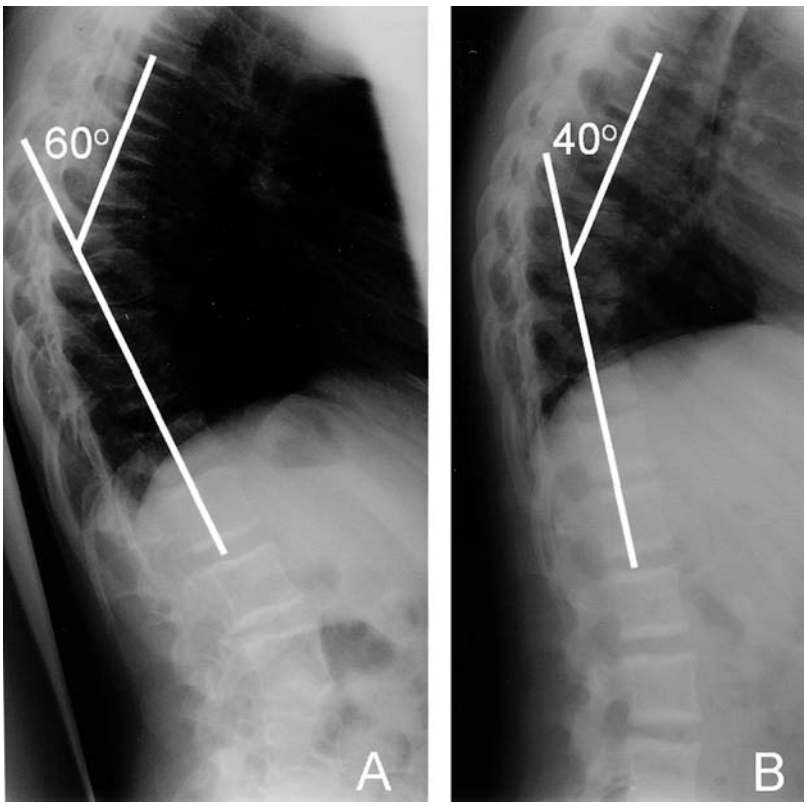

Figure 3. Patient 1: lateral spinal radiographs show improvement of kyphosis from start of pamidronate therapy (A) and at last followup 3 years later (B).

The finding of decreased bone pain in 6 out of 7 patients, which was sustained in the 4 who had ceased therapy, confirms findings in previous case series in children[8] and adults[9-11,16]. Pain relief was reported as early as a week after the infusion[11], and a single infusion was reported to relieve pain for 10 to 12 weeks[11], although most patients required repeat infusions[10]. In agreement with the case experience we describe, a lasting response was observed in most studies within 6 months of starting bisphosphonate therapy.

Bisphosphonate therapy represents a logical treatment for CRMO, as there is histological evidence of increased osteoclast and osteoblast numbers within the lesions, suggesting accelerated bone turnover. This is confirmed by the children having elevated osteocalcin levels and high normal DPD/creatinine ratio. The reduction of alkaline phosphatase and DPD/creatinine ratio suggests a reduction in bone turnover, as would be expected with PAM. A recent study observed that patients with SAPHO syndrome who symptomatically responded to PAM had significantly elevated bone turnover markers at initiation of treatment compared with nonresponders[16].

Five of the patients had evidence of spinal involvement with vertebral fractures. The etiology of the crush fractures is likely a combination of CRMO lesions within the vertebral body and reduced bone mass secondary to chronic inflammation, immobility, and corticosteroid therapy. Regardless of etiology, PAM treatment resulted in improvement of spinal BMD and vertebral shape. This has previously been described in children with osteogenesis imperfecta[14], where the structural integrity of the vertebra improves secondary to bisphosphonate therapy and modeling occurs in line with growth. We were unable to evaluate in this case series if PAM influenced spinal CRMO directly.

Synovial joint disease was unresponsive to PAM, which is in keeping with data from bisphosphonate use in other disorders associated with joint inflammation, such as rheumatoid arthritis[17]. Only one case report[18] has suggested that a joint effusion secondary to CRMO was responsive to bisphosphonate therapy; however, the patient was lost to followup soon after discontinuation of therapy.

In our series, as in the others[8], bisphosphonate therapy in children with CRMO was not associated with any significant short to medium-term side effects. Until the longterm effects of bisphosphonates in children are fully understood, all children must be monitored closely and treated within institutions with experience in the use of these medications. Potential longterm side effects include microfracture and delayed bone repair secondary to reduced bone turnover[19]. As bisphosphonates leach from bone for many years following treatment, concern has been raised regarding their use in female patients and subsequent pregnancies. A report of 2 women with osteogenesis imperfecta who became pregnant after 5 years of PAM therapy showed no maternal complications. It could not be excluded, however, that the adverse events noted in the babies, hypocalcemia and talipes equinovarus, were related to maternal treatment of pamidronate therapy[20]. Osteonecrosis of the jaw has been reported in adults treated with bisphosphonates[21]. There have been no reports in children, but children should have regular dental review while treated.

Although a randomized trial of bisphosphonate use in CRMO is lacking, and the retrospective data presented here have potential limitations, we feel bisphosphonate use should be considered early in a child with CRMO for pain relief and in those with disease affecting the spine. For subjective improvement our experience suggests a short course of bisphosphonate therapy (3 to 6 months) may be all that is required. A prolonged course of treatment is suggested in patients with reduced bone mass or in patients with vertebral fractures until there is evidence of significant modeling. Further studies are needed to confirm whether bisphosphonate therapy can lead to resolution of nonspinal lesions.

ACKNOWLEDGMENT

The authors acknowledge the referral of patients from Dr. Neville Howard of the Institute of Endocrinology and Drs. Ian Barrett and David Little of the Department of Orthopaedic Surgery, The Children's Hospital at Westmead, and Don Anderson, John Hunter Hospital, Newcastle, Australia.

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