A standardised clinical and radiological follow-up of patients with chronic non-bacterial osteomyelitis treated with pamidronate

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Abstract

Objective

Chronic non-bacterial osteomyelitis (CNO) is an autoinflammatory disorder of the skeletal system. Treatment with NSAIDs is generally effective in the majority of patients, however, a sizeable proportion of patients have persistent disease and subsequent treatment strategies are required. The aim of this study was to characterise the clinical and radiological disease course in CNO patients treated with the bisphosphonate pamidronate (PAM).

Methods

Eight CNO patients refractory to NSAIDs, glucocorticoids and sulfasalazine were treated with 6 cycles of PAM in four-weekly intervals. The disease course was assessed by clinical examination and whole-body (WB) MRI at standardised time points during the treatment phase and in a 6 months follow-up.

Results

Seven patients were in complete clinical remission after 6 applications of PAM. WB MRIs showed regression of inflammatory lesions in 7 patients with complete remission in only one patient and partial remission in 6 patients. One patient developed radiological progression despite a marked improvement of clinical symptoms. In the follow-up after PAM therapy, 3 patients developed MRI confirmed relapse. Additional applications of PAM induced a sustained clinical remission and partial radiological response in two of them. Mild temporary adverse effects were noted in 5 patients.

Conclusion

Our study highlights that PAM is effective in controlling clinical symptoms (e.g. pain) in CNO patients. However, subclinical bone inflammation was still detectable by MRI in most of the patients and disease progression was noticed in some patients after cessation of PAM.

Key words

chronic non-bacterial osteomyelitis, pamidronate, inflammation, MRI

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Introduction

Chronic non-bacterial osteomyelitis (CNO) is an inflammatory, non-bacterial disorder of the skeletal system of yet unknown etiology, predominantly affecting the metaphyses of long bones, the pelvis, vertebral bodies and the clavicle in children and adolescents (1-2). However, lesions can occur at almost any site of the skeleton except the neurocranium. Patients usually present with local bone pain, localised inflammation with swelling and warmth and often suffer from functional impairment. Associated extra-osseous symptoms have been reported, including palmo-plantar pustulosis, psoriasis and inflammatory bowel disease (2). Histological and microbiological analyses indicate a sterile chronic inflammation with cellular infiltration of neutrophils, lymphocytes and monocytes, leading to an increased osteoclastic bone resorption with concomitant sclerosis and fibrosis and also cortical hyperostosis (3-4). The extent of CNO may range from a single lesion to the most severe form of CNO, called chronic recurrent multifocal osteomyelitis (CRMO), characterised by extended multifocal, often symmetrical, inflammatory lesions with an undulating time course (3-4). Whole-body magnetic resonance imaging (WB-MRI) has been proven to be most useful for diagnosis and follow-up of CNO (5).

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly the first-line therapy for CNO and achieve pain-reduction in most patients, however, generally accepted treatment protocols or guidelines for CNO are not available (6). Long-term follow-up of patients with CNO has documented a favourable outcome with resolution of symptoms in the majority of patients. Nevertheless, a significant fraction of patients is affected by persistent disease (up to 25%) and requires treatment concepts in addition to NSAIDs (1). Second-line treatment includes glucocorticoids, disease-modifying antirheumatic drugs (DMARDs, *e.g.* sulfasalazine) as well as cytokine-blocking agents (2, 6-7). Bisphosphonate (BP) treatment has also been reported in retrospective case reports or small series for treatment of refractory CNO (8-12). BPs are the mainstay of medical therapy in the fracturing child with primary or secondary osteoporosis or impairment of bone structure (13-14). The vast majority of data published concerning PAM treatment in childhood correlates with *i.v.* pamidronate (PAM) use in children and adolescents with severe osteogenesis imperfecta. PAM is a powerful inhibitor of osteoclasts with pain-modifying and anti-inflammatory effects. Therefore, it seems to be a suitable candidate for use in CNO patients with persistently active CNO disease course despite conventional treatment.

Here, we present our follow-up cohort of eight children with severe refractory CNO assessing clinical and radiological outcomes in the course of six applications of PAM.

Materials and methods

Eight patients (7 female), who had been diagnosed with CNO at the Children's hospital, University of Würzburg, Germany were included in this follow-up. All patients were diagnosed using a recently published standardised diagnostic protocol regarding typical clinical symptoms (pain, local swelling and/or limited motion), histology (inflammation and/or fibrosis or sclerosis with exclusion of malignant process), microbiology (negative culture and eubacterial PCR) and imaging (MRI) (6). The mean age at diagnosis was 15.8 years (range 5–17).

None of the patients had a satisfactory outcome with previous anti-inflammatory treatment already including second line agents in addition to NSAIDs. PAM was used as off-label medication and administered intravenously in a hospital setting. Written informed consent of the patients and/or parents was obtained. The patients were treated with PAM 1 mg / kg body weight every 4 weeks for 6 months (six applications) with a maximum dose of 60 mg per cycle while continuing to receive their previous medication. In case of minor adverse effects, the PAM dose was reduced by 50%.

The patients were evaluated clinically every 4 weeks after PAM infusion using a standardised protocol assessing

Table I. Clinical characteristics of study patients.

Patient	Sex	Age at diagnosis (onset of symptoms)	Number of affected bones	Locations	Treatment before PAM	Duration of treatment before PAM	Comorbidities/ problems
1	F	9y	1	rigt mandible	NSAID, Pred	4y	neurofibromatosis, PAS
2	F	14(10) y	1	right clavicle	NSAID, Pred	2y	PAS
3	F	17(15) y	1	sternum	NSAID, Pred, Sulf	4m	OA
4	F	16(13) y	3	ossa ilia	NSAID, Pred, Sulf	3y	psoriasis
5	F	17(14) y	4	sternum, left clavicle, rib, lumbar vertebra (L2)	NSAID, Pred, Sulf	4y	–
6	F	16y	3	femura, left tibia	NSAID, Pred, Sulf	3y	obesity
7	F	9y	12	spine, Th6-11, S2/3, left femur, feet	NSAID, Pred, Sulf, Aza, Mesa	3y	Crohn's disease
8	M	5y	12	femura, tibiae, ossa ischii, calcanei, rib, left ulna, AC-joint	NSAID, Pred, Sulf, ETA	9y	obesity, OA, incompliance

Y: years; m: months; L: lumbar; Th: thoracic; S: sacral; NSAIDs: non-steroidal anti-inflammatory drugs; Pred: prednisolone; Sulf: sulfasalazine; Aza: azathioprine; Mesa: mesalazine; ETA: etanercept; PAS: pain amplification syndrome; OA: oligoarthritis.

pain, clinical signs of inflammation and impairment of everyday life. Complete clinical remission was defined as absence of pain and clinical signs of inflammation. Partial clinical remission was defined as improvement of pain and/or clinical signs of inflammation without complete absence of these symptoms.

WB-MRI was performed before, after three and six cycles of PAM therapy on a 1.5 Tesla scanner (Magnetom Symphony, Siemens Healthcare AG, Germany) as described recently (5). It included non-enhanced T1w TSE, post contrast (Gd-DTPA, Magnevist®, Bayer Schering Pharma, Germany, 0.2 ml/kg body weight) fat saturated T2w TSE and T2w TIRM sequences with a section thickness of 4 mm. Inflammatory lesions were defined by an increased signal on T2wTIRM, hypointensity on T1w and post-contrast lesional signal elevation. Complete radiological remission was defined as absence of signs of inflammatory lesions (as defined above) and partial radiological remission was defined as regression of inflammatory lesions in number and/or size in MRI analysis. An increase of the number or size of inflammatory lesion was defined as radiological progression. Relapse was defined as reoccurrence of characteristic clinical symptoms and detection of new lesions by MRI in a patient that has been in remission before.

Results

Clinical characteristics

The clinical characteristics of each patient are outlined in Table I. Three patients showed unifocal lesions (mandible, clavicle or sternum) and 5 patients had multifocal lesions (range 3–12 radiologically defined lesions). The patient group showed a disproportionately high number of patients with sterno-clavicular or spinal affection. Distribution of symptomatic regions was the following: clavicle 2, vertebral column 9 (6 thoracic, 1 lumbar, 2 sacral), arm 2, rib/sternum 4, pelvis 6, thigh/lower leg 8, foot 5, visceral cranium 1. All patients suffered from severe pain and functional impairment, which affected everyday life activities. One patient became bound to a wheelchair; another one had pathological fractures in several vertebral bodies requiring an orthopedic corset. Significant comorbidities included oligoarthritis (2), psoriasis (1) and neurofibromatosis (1). One was diagnosed with Crohn's disease one year after the diagnosis of CNO. Obesity (2) and incompliance in *p.o.* medication intake (1) were further problems. All patients were treated with NSAIDS and low dose prednisolone *p.o.*, 6 patients additionally received sulfasalazine, one patient in addition azathioprine and mesalazine due to Crohn's disease and another one in addition etanercept. Mean duration of treatment before starting PAM was 3 years (range 0.4–9.0). In 4 patients the time between onset of symptoms and diagnosis with consecutive start of treatment was delayed (2–4

Table II. Outcome of patients treated with pamidronate.

Patient	Adverse effects	Outcome after 6 x PAM		Outcome 6 months after last PAM	
		Clinical	Radiological	Clinical	Radiological
1	–	CR	PR	CR	PR
2	nausea	CR	PR	CR	PR
3	phlebitis	CR	CR	CR	CR
4	headache	CR	PR	CR	PR
5	–	CR	PR	PROG	PROG
6	nausea, fever, phlebitis	CR	PROG	lost to follow-up	
7	–	CR	PR	PROG	CR
8	fever, nausea arthralgia	PR	PR	PROG	PR

PAM: pamidronate; CR: complete remission; PR: partial remission; PROG: progression.

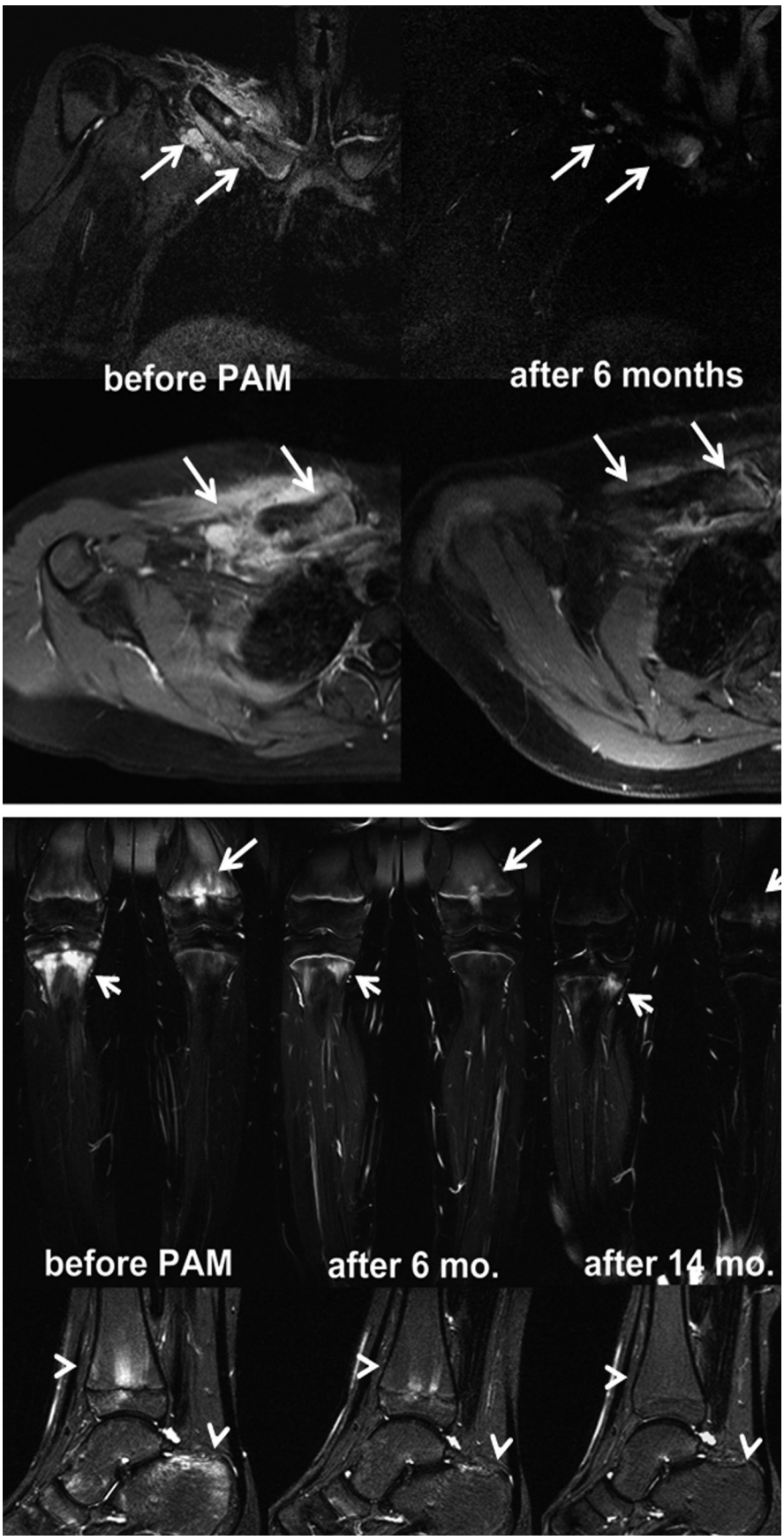

Fig. 1. MRI follow-up examinations of two patients with CNO (patient 2 and 8) treated with pamidronate.

The upper set of four images shows a CNO manifestation at the right clavicle in a 14 year-old girl (coronal T2w TIRM and transversal contrast-enhanced T1w TSE with fat saturation). The intraosseous and perifocal soft-tissue oedema and contrast enhancement seen prior PAM treatment is markedly reduced after therapy with remaining focal intraosseous signal alterations in the medial clavicle (long arrows).
The lower set of images depicts genual, tibial and tarsal CNO manifestations in a 12 year-old boy (coronal and sagittal T2w TIRM, left hand side). Marked response to treatment was noted after six months of PAM treatment (middle), indicated by a decrease of bone marrow oedema. On further follow-up at 14 months (right hand side), complete remission of distal tibial and calcaneal CNO foci was observed (arrow heads), while some amount of focal bone marrow oedema persisted in the right proximal tibia (short arrows). A CNO lesion in the left distal femur (long arrows) showed persistent signal elevation over the course of the study but was not fully included in the presented cross-sections of follow-up MRI.

years). The previously given medication was continued during PAM therapy, except for etanercept.

Outcome of patients treated with PAM

In all patients PAM treatment induced rapid improvement of pain, local swelling and functional impairment resulting in complete clinical remission in 7 of 8 patients and partial clinical remission in one patient after 6 applications. All patients recovered full function, patient 7 regained normal activity without any further need for the wheelchair and those who had absences at school due to CNO related pain returned back to school regularly. The outcome of each patient is outlined in Table II. Mild temporary adverse effects were noted in 5 patients including nausea (3), phlebitis at the injection site (2) headache (1), fever (1) and arthralgia (1). No severe adverse effects were noted (*e.g.* osteonecrosis of jaw or symptomatic hypocalcaemia). Dose reduction was performed in 3 patients (patient 3, 6 and 8) who subsequently showed a good tolerability of PAM. In summary, in our case series PAM was well tolerated and patients with refractory CNO showed an immediate and good clinical response to PAM therapy.

Follow-up MRIs during and at the end of PAM therapy showed marked regression of signs of inflammation in 7 patients. However, after 6 administrations of PAM complete radiological

remission was achieved in only one patient. 6 patients – albeit 5 of them being in complete clinical remission– still showed MRI signs compatible with active inflammation after 6 cycles of PAM treatment (Table II, Fig. 1). In one of these partial responders (patient 5) one new radiological lesion could be detected which was clinically silent. One patient (patient 6) showed radiological progression after 6 cycles of PAM despite of marked clinical improvement.

We conclude that the radiologically defined disease course in CNO patients under PAM treatment does not parallel the clinical disease course and that patients in complete clinical remission may still show signs of active inflammation in MRI. Nevertheless, the refractory CNO patients in our series showed a favourable response to PAM treatment based on MRI finding.

We were able to follow 7 of the 8 treated patients after completion of 6 applications of PAM treatment for an extended period (Table II). Patient 6 – who showed radiological progression – denied further treatment and was lost to follow-up 3 months after last PAM. At follow-up 6 months after the last PAM treatment 4 of the 7 patients did not show any clinical or radiological signs indicative for a relapse. Patient 8 complained about minor pain in the calcaneus (partial radiological remission), patient 7 about chronic back pain due to residuals of vertebral fractures (complete radiological remission but radiological damage). Patient 5 developed clinical and radiological relapse with recurrent strong back pain and new radiological lesions in L3, Th11.

In the longer follow-up 2 further patients developed clinical and radiological relapse (patient 4 after 12 and patient 8 after 18 months). Three patients received additional applications of PAM starting at the time of relapse (patient 4 one, patient 5 three, and patient 8 two applications after 12, 6 and 18 months) resulting in sustained clinical remission and partial radiological response in two of them. In patient 5 PAM did not achieve clinical and radiological remission, therefore etanercept was initiated resulting in limited success with partial clinical and radiological remission after 6 months of treatment.

In summary, the overall good clinical and radiological response to PAM treatment observed in our study cohort was sustained in the early phase after PAM treatment (<6 months). However, some patients did not achieve long-term remission and showed radiological signs of inflammation even under long-term PAM treatment.

Discussion

We report herein a standardised clinical and radiological follow up of patients with severe chronic CNO treated with PAM. All of the patients had a bone biopsy, which did not show histological signs of malignant disease or microbiological indicators of an infectious process. Therefore, it makes it rather unlikeley that the bone affection in the described patients may be explained by another disease mimicking CNO (*e.g.* Langerhans cell histiocytosis).

All eight patients showed considerable pain relief after initiation of PAM treatment. Clinical remission was paralleled by an improvement of bone inflammation in all but one patient as documented by WB-MRI. However, complete radiological remission could not be achieved under PAM treatment in the majority of the patients and relapses occurred in some patients after cessation of PAM.

Although clinical outcome of children with CNO is generally good and treatment with NSAIDS is effective in the majority of patients, a sizeable proportion of patients have persistent disease. Therefore, more intensive treatment strategies are required to prevent skeletal damage in the long run. However, evidence based treatment strategies with second-line drugs are sparse in patients with limited success of NSAIDs. BPs, namely PAM, have been used in earlier retrospective case series especially for CNO patients with spinal involvement (8-12). PAM treatment was associated with pain resolution, improvement in vertebral height and shape as well as in spinal bone mineral density (9-10). In all of these retrospective reports different dosing regimens have been used and there is no consensus on the dosage and duration of PAM treatment in CNO. We aimed to use a standardised treatment regime for all reported CNO patients, which was adopted from protocols established for treatment of osteogenesis imperfecta (13). Although designed as a follow-up, the good clinical response of the CNO patients to PAM treatment in our study has to be discussed cautiously due to a missing control group and some tendency of spontaneous regression in CNO. However, the close temporal relationship between PAM administration and improvement of clinical symptoms support a significant therapeutic effect. Given the moderate response to conventional treatment before PAM initiation, the pronounced amelioration of clinical symptoms was a major improvement for the patients. However, a placebo-controlled study is strongly needed to finally ascertain the efficacy of PAM treatment in CNO.

Interestingly, the disease course as assessed by clinical observation did not correlate with the radiological MRI findings in the treated patients. All except one patient showed complete clinical remission but only one patient developed complete radiological remission after six cycles of PAM treatment. Therefore, PAM treatment seems to effectively control pain as a major clinical symptom of CNO patients, however, the effects of PAM on bone inflammation (as assessed by MRI) seems to be either less pronounced or may rather develop in a longer time frame. The mechanism of action of PAM in inflammatory bone diseases is only partially understood. BPs show a high affinity to hydroxylapatite and their accumulation in bone results in osteoclast inhibition and apoptosis (15). Second generation amino-BPs, like PAM, act on bone metabolism by specifically blocking the farnesyl pyrophosphate synthase in the mevalonate pathway resulting in inhibition of protein prenylation of *e.g.* small GTP binding proteins and thereby impinging on the bone-resorbing activity and survival of osteoclasts. Anti-inflammatory properties of BPs might be explained by acting on myeloid cells, thereby modulating the expression of inflammatory cytokines,

especially TNF-α, interleukin-1 and 6. Since inflammation induced bone resorption and hyperactivity of myeloid cells is a hallmark of CNO, it is tempting to speculate that PAM treatment may beneficially modulate the long-term course of CNO patients by inhibiting the discussed mechanisms. Additionally, analgetic effects of BPs have been demonstrated in patients with bone metastases probably due to their direct inhibition on osteoclast-mediated bone resorption.

In our study PAM treatment was not associated with any severe adverse effects. Mild transient acute phase reactions were noted in 5 patients resulting in dose reduction in three of them. Two of these patients showed an unfavourable disease course in the long-term. However, due to the small numbers of patients included in our case series we can only speculate whether higher PAM doses or a prolongation of the treatment might be superior in achieving remission or in avoiding relapses. Atypical fractures and osteonecrosis of the jaw have been reported in adults treated with PAM, but did not occur in our presented patients so far. Since BPs have a long half-life in the skeleton concerns have been raised regarding their use in female patients and subsequent pregnancies. This is noteworthy since CNO is largely biased towards the female sex and correlates with disease onset at adolescence.

In conclusion, our study highlights that PAM is effective in controlling clinical symptoms and in particular pain in children and adolescents with refractory CNO. However, subclinical bone inflammation was still detectable by MRI in most of the patients and disease progression was noticed in some patients after cessation of PAM. Future collaborative efforts should aim on analysing the significance of BPs in comparison to other second-line drugs used in CNO and in optimising multimodal treatment regimen for patients with CNO.

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