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Original article

Treatment of chronic recurrent multifocal osteomyelitis with bisphosphonates in children

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ABSTRACT

Objectives: Assessment of bisphosphonates efficiency in the therapy of NSAIDs-refractory Chronic Recurrent Multifocal Osteomyelitis.
Methods: Retrospective analysis of records of patients treated for Chronic Recurrent Multifocal Osteomyelitis between 2012 and 2018.
Results: Between 2012 and 2018, 76 children and adolescents were diagnosed with Chronic Recurrent Multifocal Osteomyelitis in our department. All patients underwent an initial course of NSAIDs therapy that provided a remission in 46% of cases. Of 41 NSAIDs-resistant cases, 7 patients were male and 34 were female. Disease started meanly in the age of 10. Most frequently pain localised in foot, clavicle and hip. In presented group, pamidronate was administered intravenously in the dose of 1 mg/kg/day for 3 days. Patients received 6 series (1–17 series) on average with mean interval of 10 weeks (4–14 weeks). Our observations demonstrated rapid decrease of symptoms intensity after first dose of pamidronate with relapse of pain after 3–4 weeks. The frequency of pamidronate dosage was dependent of patient's symptoms. No serious adverse effects were reported. We finished the therapy after complete remission of symptoms and complete bone remodelling in imaging. Of 41 patients, 32 achieved remission and 9 continue their therapy. In remission group patients received 7 series of pamidronate on average and their treatment lasted meanly 20 months.
Conclusions: Pamidronate is a safe and efficient method of CRMO therapy, particularly in cases refractory to NSAIDs treatment. Treatment with pamidronate provides both symptomatic relief as well as normalisation of bone morphology.

1. Introduction

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a disease that may lead to significant impairment of life quality in children and adolescents. Although it is considered a rare condition, some studies show that it may be as common as infectious osteomyelitis [1,2]. Initially it was believed to be a form of infectious osteomyelitis, but lack of microbiological findings and resistance to antibiotical treatment neglected this theory. Current studies focus on the onset of CRMO as a result of imbalance between proinflammatory (TNF-α, Il-20, Il-6) and anti-inflammatory (Il-10, Il-9) factors [3]. Genetical component of this disease is also highlighted due to its monogenetic forms (Majeed syndrome, IL-1 receptor antagonist deficiency) and a significant association with the susceptibility gene on chromosome 18 [4].

Various attempts were made to establish standards of treatment of CRMO. Initial management consists in treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) [5]. In case of insufficient response for NSAIDs, various agents are used, including bisphosphonates, TNF inhibitors and non-biologic DMARDs such as methotrexate or sulfasalazine [6]. Although therapy of NSAIDs-refractory CRMO with bisphosphonates becomes increasingly popular, evidence of bisphosphonates efficiency is based mostly on small case series [7–10] or retrospective studies without major emphasis on bisphosphonates [11–13]. Therefore, we decided to perform a retrospective analysis of the large cohort of CRMO patients treated with pamidronate.

The objective of our study was to analyse clinical signs of CRMO and evaluate outcomes of treatment with pamidronate.

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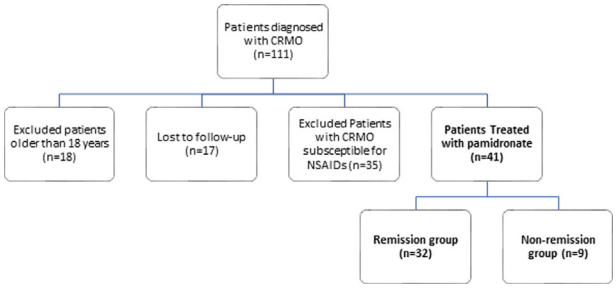

Fig. 1. Flow chart of patients' selection with exclusion criteria.

2. Methods

We retrospectively analysed data of CRMO patients treated in our department between 2012 and 2018. Analysed data included patients' hospital records, outpatient department records, results of imaging and laboratory values. The diagnosis of CRMO was made according to criteria described by Jansson et al. [14]. Patients older than 18 years old and susceptible for NSAIDs treatment were excluded from further analysis. Patient selection process is presented in Fig. 1.

Collected data comprised patients' demographic characteristics, symptoms of the disease, course and outcomes of treatment. All patients underwent an initial course of NSAIDs therapy, which lasted 4 weeks as recommended by Zhao et al. [6]. In cases with previous history of CRMO therapy with NSAIDs in other departments, we considered failure of shorter, 2 week's long initial trial as an indication to begin second-line therapy. After failure of NSAIDs treatment, pamidronate was used in the 3-day protocol applied previously in treatment of osteogenesis imperfecta [15]. We administered pamidronate intravenously in the dose of 1 mg/kg/day for 3 consecutive days. Such sequence was repeated every 12 weeks until remission was achieved. The frequency of pamidronate administration was modified basing on intensity of patient's symptoms. We defined remission as a lack of anti-inflammatory treatment, absence of clinical symptoms and complete healing of bone lesions in radiological examination.

Extensity and activity of the disease was assessed using several imaging modalities. Initial examination included radiograph of the painful area, followed by bone scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI), which permitted comprehensive evaluation of patient's state. In atypical cases, diagnosis was confirmed by histopathological analysis of suspected bone lesion.

Pearson correlation was used to compare correlation between amount of received pamidronate sequences and potential influencing factors. Statistical analysis was performed using Statistica version 12 software (StatSoft Inc., Jagiellonian University license).

2.1. Role of the funding source

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sector.

3. Results

3.1. Demographics and clinical characteristics

Between 2012 and 2018, 41 patients with diagnosed CRMO were treated with pamidronate. Analysed groups consisted in 7 boys (18.6%) and 34 girls (81.4%). Median age at the onset of disease was 10 years (5–14 years). The characteristic of these patients is summarized in Table 1.

Table 1
Characteristic of CRMO patients treated with bisphosphonates.

Age at the onset of symptoms, mean (years)	10
No. female/male	34/7
Clinical localisations per patient, mean	2.83
Radiologic lesions per patient, mean	1.93
ESR, mean (mm)	18.3
CRP, mean (mg/l)	8.6
Amount of patients with performed radiologic examinations	
MRI	17
CT	26
Bone scintigraphy	26
Unifocal form of CRMO (No. of patients)	12
Axial localisation of lesions (No. of patients)	23

The main localisation of pain was foot (43.9%), clavicle (43.9%) and hip (36.59%). Localisation and frequency of other lesions are presented at Fig. 2. Mean amount of symptomatic lesions was 3 per patient. In cases with multifocal presentation, onset of the disease was mostly associated with symptoms in clavicle (24.32%), mandible (16.22%) and foot (13.51%) – Fig. 3. Spinal involvement was diagnosed in 8 (19.5%) patients.

3.2. Radiological findings

Radiographs indicated lesions in 10 patients. Typical findings were broadened bone contour, discrete lytic lesions and slight lamellated periosteal reaction. The majority of patients had scintigraphy performed, which indicated alterations in 26 (63.4%) cases. MRI was performed in 17 (41.4%) patients. The typical presentation of lesions in MRI was bone marrow oedema together with hypointensity in T1-weighted sequence and hyperintensity in T2-weighted sequence. Overall, 30 (73%) patients have whole-body imaging done. 26 (63.4%) of patients exhibited findings of CRMO in computed tomography with numerous, little lytic lesions surrounded by sclerotic bone and, rarely, with widening of bone contour.

3.3. Correlation of patients symptoms with radiological findings

Overall patients had 147 lesions, of which 68 was diagnosed only clinically, 49 was symptomatic lesions confirmed radiologically and 30 was asymptomatic lesions diagnosed only with imaging. The majority of symptomatic lesions undiagnosed radiologically was localised in foot. The most common localisation of asymptomatic lesions was clavicle and ilium. The correlation of patients' symptoms with radiological findings is presented at Fig. 4.

3.4. Bone biopsy

In case of atypical presentation, bone biopsy of the lesion was performed to exclude malignancy. 13 (31.7%) of our patients underwent histopathological analysis, which confirmed the diagnosis of CRMO. Typical findings included inflammatory changes with moderate fibrosis and presence of neutrophils and lymphocytes.

3.5. Treatment outcomes

Of 41 patients, 32 achieved remission and 9 patients continue therapy. The median number of infusion cycles needed to achieve a remission status was 7.16 (1–17 sequences). The distribution of dose amounts is presented at Fig. 5. Median interval between doses was 10 weeks. After first year of therapy, 31.2% of patients achieved remission. Initially, second dose was administered 4–5 weeks after the first one and then the interval between following doses was gradually prolonged until target interval of 12 weeks was achieved.

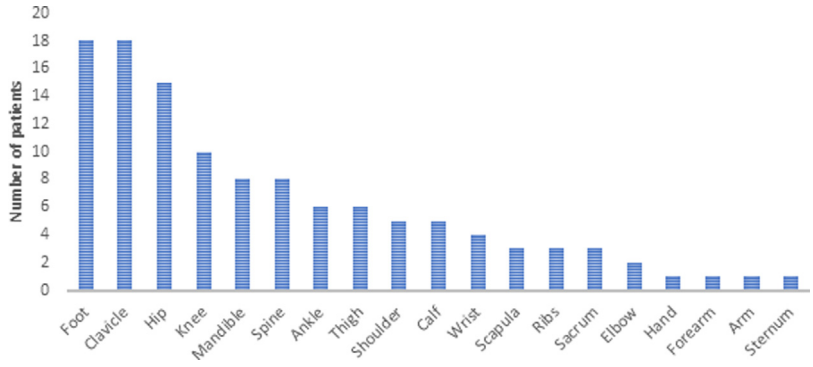

Fig. 2. Localisation of symptomatic lesions.

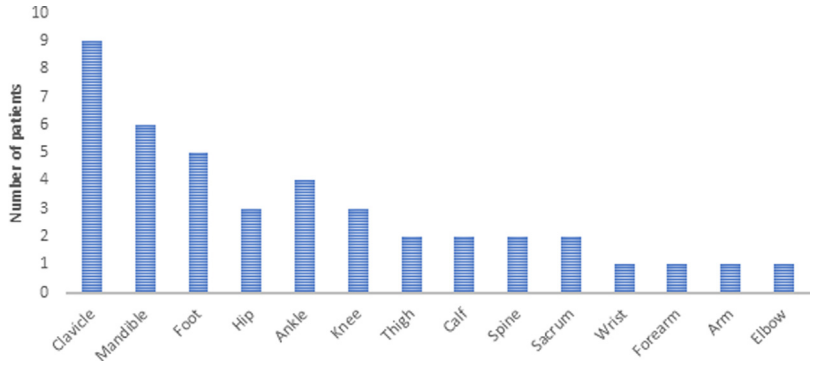

Fig. 3. Primary localisation of symptomatic lesions.

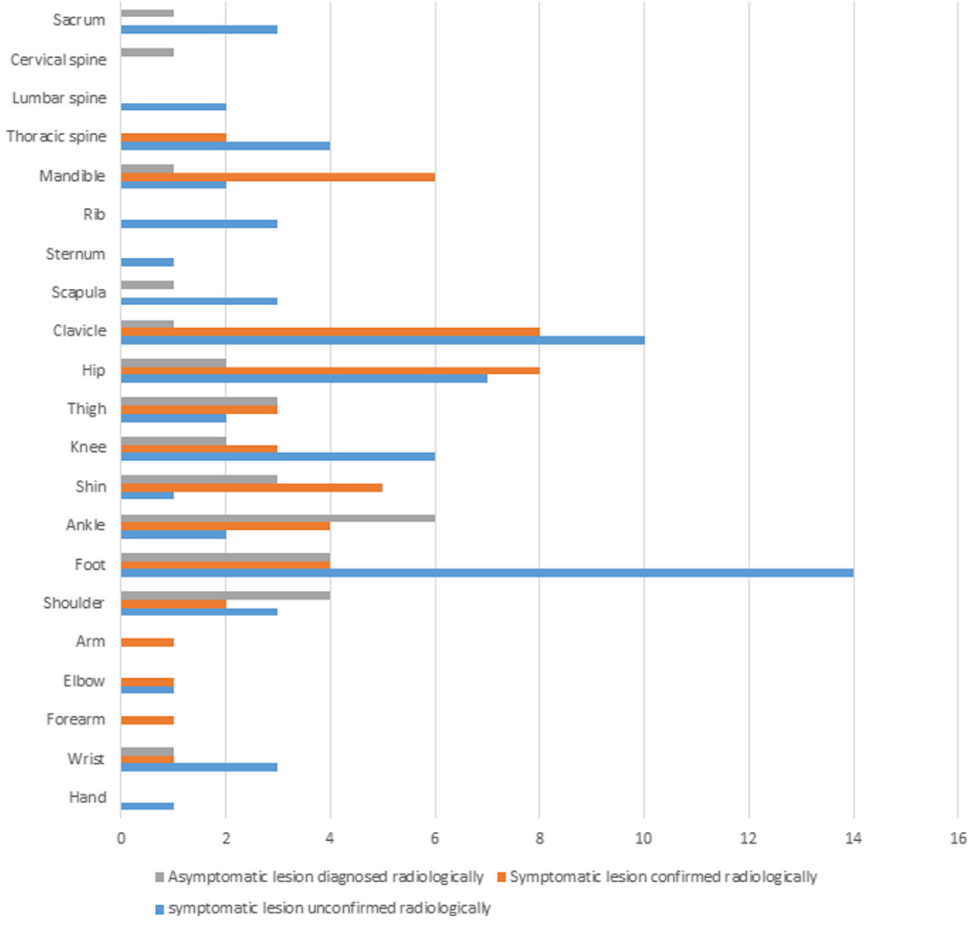

Fig. 4. Relationship of patients' symptoms with radiological findings.

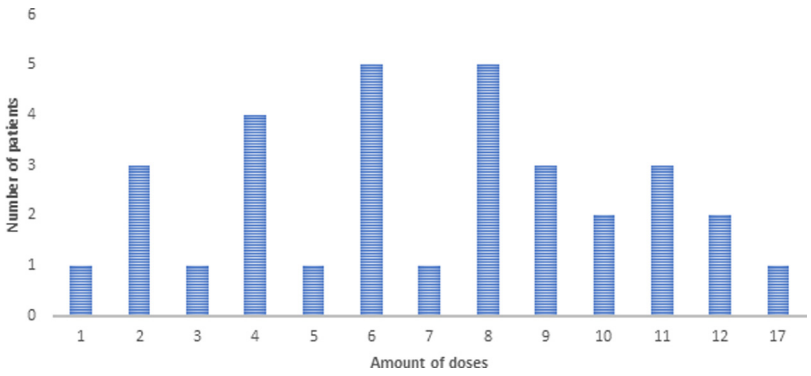

Fig. 5. The distribution of the amount of doses.

Table 2
Correlation between length of therapy and clinical factors.

Factor	Correlation coefficient
Age	0.119149
Male sex	−0.109920
Amount of lesions in medical imaging	−0.080859
Multiple lesions in medical imaging	−0.216260
Localisation of the lesions	
Lesions localised in axial skeleton	−0.065216
Lesions localised in appendicular skeleton	0.031214
Lesions localised both in axial and appendicular skeleton	0.039507

0.10–0.29: weak correlation; 0.30–0.49: moderate correlation; > 0.50: strong correlation; none of the correlations appeared to be statistically significant.

Currently mean follow-up in remission group is 21 months (8–45 months) with no relapse of symptoms.

In non-remission group, patients received 3.33 pamidronate sequences (1–7 sequences) on average. Median interval between doses was 8.5 weeks (4–12 weeks). The majority of patients in non-remission group was diagnosed later than those in remission group and currently all patients in non-remission group continue pamidronate therapy.

The analysis of correlation between amount of pamidronate doses and potential influencing factors is given in Table 2. None of analysed variables appeared to correlate with the length of the therapy.

4. Discussion

Recently bisphosphonates gained recognition as one of the most effective second line treatment of CRMO after NSAIDs failure [10,13,16]. Reported efficiency of treatment varies between authors, however small amounts of treated patients and variety of clinical endpoints preclude direct comparison. Currently published data from multicentre study basing on Eurofever International Registry [17] suggest that complete response may be achieved in 51% of patients with only 3% of patients defined as non-responders. In another multicentre report published by Bhat et al. [18] patients responded to treatment with bisphosphonates in 68.5% of all cases. That corresponds with our results in which 31.25% of patients achieved remission within first year of treatment. In our group amount of NSAIDs-susceptible patient was relatively high (54% of all treated paediatric CRMO patients) comparing to other authors [5]. Although some authors suggest assessment of patient's response after 3 months [6], it is generally accepted that treatment with pamidronate should last 9 months [19]. Interestingly, in our remission group mean duration of treatment was 20 months. That may suggest longer treatment period that is needed before defining a patient as a responder or a non-responder.

The choice of the optimal bisphosphonate agent remains subjective as there is no randomized trials comparing effects of therapy between each drug in children [20]. Because pamidronic acid was the first bisphosphonate to be used in children and the evidence of its efficiency and safety is the greatest, it has been chosen in our group of patients. However, growing evidence shows beneficial effects of treatment with zoledronic acid [21] and recent recommendations suggest that this agent may be suitable as well [6].

First dose of pamidronate frequently caused rapid decrease of pain level leading even to complete remission of symptoms. However, after 2–3 weeks we observed relapse of symptoms, hence we decided to routinely administer second dose of pamidronate 4–5 weeks after the first one.

While comparing remission and non-remission group in our study it is evident that amount of doses in non-remission group is significantly lower (7.16 doses in remission vs. 3.33 doses in non-remission group). Thus, we cannot define non-remission group as non-responders as they still continue their therapy.

Current evidence demonstrates long-term safety and good tolerance of pamidronate in paediatric population. The most commonly described adverse events included bone pain, headache, fever and electrolyte abnormalities [22,23]. Till now, osteonecrosis of the jaw was not reported in any children or adolescent [16,18]. Despite the impact on bone remodelling, bisphosphonates do not harm growing skeleton or impair the normal growth [24]. Similarly during treatment of described cohort, no serious adverse effects were reported. The majority of patients complained of mild flu-like symptoms (including fever and headache), particularly during administration of the first dose of pamidronate. Regardless that, it is mandatory to assess calcium level after administration of pamidronate due to the risk of hypocalcaemia. Furthermore, some authors suggest periodic oral cavity control in prevention of jaw osteonecrosis [16].

Demographic characteristic of our cohort do not differ significantly of those described by other authors. The majority of our patients were girls and onset of the disease tended to happen between first and second decade of life as described in other reports [11,14] and reported previously by one of the authors [25].

Plain radiograph is usually the first imaging performed during admission of the patient despite the non-specificity of alterations revealed in this modality [26]. Lack of findings characteristic for malignancy may suggest diagnosis of CRMO. However, plain radiographs indicate only 16% of lesions diagnosed in other modalities [27]. Recently MRI is considered an essential imaging modality in management of CRMO due to the high sensitivity in assessment of bone oedema and inflammation [2,10,28]. Typical presentation of CRMO in MRI is an ill-defined, edema-like lesion with lack of cyst-like components [27]. In our experience MRI is particularly useful in diagnosing lesions localised in vertebrae, allowing complex

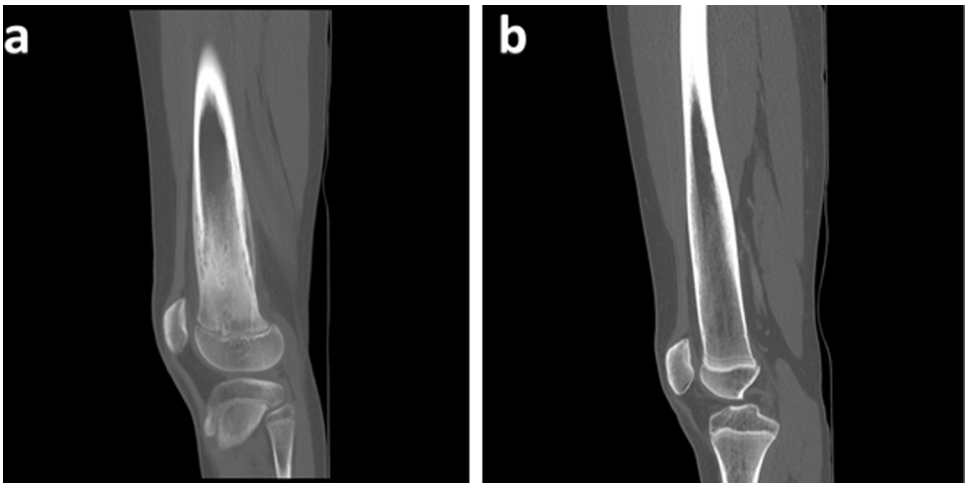

Fig. 6. Lesion of the distal femur in the course of CRMO: a) before treatment with pamidronate; b) after treatment with pamidronate.

evaluation of extensity and activity of this changes. Furthermore, MRI and bone scintigraphy are essential in evaluating the multifocal involvement in CRMO [10,26,29]. Although MRI is considered the gold standard in evaluation of multifocal involvement in the course of CRMO, recent publications consider bone scintigraphy an adequate alternative if MRI availability is limited [6,27]. However, MRI is preferred over bone scans or CT as it avoids exposure to radiation [18]. Computed tomography is not a modality of choice in imaging of CRMO, but its excellent spatial resolution permits precise definition of completed bone healing. Initially, CRMO lesions present with many little lytic foci surrounded by sclerotic bone (Fig. 6). The contour of the affected bone is often broadened and cortical bone may be thickened. Treatment with bisphosphonates remodels lytic lesions, recreates normal bone microstructure and relieves bone sclerotisation and oedema.

In chronic patients with fluctuating course of CRMO each new onset of pain in previously unaffected region was not considered as indication for imaging. Therefore the amount of lesions diagnosed only clinically is relatively high. Surprisingly, the most common localisation of pain was foot. However, these symptoms was not confirmed radiologically. As the percentage of clinically silent lesions of tibia and fibula is greater than symptomatic ones, part of these lesions may cause pain perceptible at the foot.

Although clinicians become increasingly aware of symptoms and treatment of CRMO, management of this condition in daily practice still leaves a lot to be desired [2]. Frequent cause of hospitalisation was suspicion of malignancy or osteomyelitis. Even if such a diagnosis was excluded, often several biopsies from other lesions were performed. Attempts to treat this condition in secondary care units included surgical management, even excision of the lesions with subsequent reconstruction with bone grafting. It has to be clearly stated that such procedures are strictly contraindicated.

Our study has several limitations. The retrospective character of this analysis precludes unified research protocol and generates missing data. Moreover, both imaging examinations and bone biopsies were performed basing on clinical situation, what is potential source of bias during analysis. Therefore, this data should be treated with caution as they was not profoundly analysed.

Disclosure of interest

The authors declare that they have no competing interest.

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