

Effectiveness of treatment with intravenous pamidronate for calcinosis in juvenile dermatomyositis

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Abstract

Objective

Calcinosis is a frequent finding in up to 40% of children with juvenile dermatomyositis (JDM). Different treatments (aluminum hydroxide, diltiazem, probenecid, alendronate, etc.) have been used in an attempt to clear calcinosis and to avoid the onset of new calcium deposition, but none has been clearly effective. Pamidronate is a nitrogen-containing bisphosphonate with a potent inhibiting bone resorption effect that has been used to treat osteoporosis in children. We report three children with JDM who developed calcinosis and who received intravenous pamidronate with good results.

Methods

All three patients met the Bohan and Peter diagnostic criteria for JDM. Intravenous pamidronate was given at 1 mg/kg/day on three consecutive days every three months according to the protocol established by Glorieux et al. for osteoporosis treatment in osteogenesis imperfecta.

Results

The calcinosis which developed in all three patients improved. No important adverse events were observed.

Conclusion

In all three cases, calcinosis significantly decreased, and even totally cleared in patient 1. Total clearance of pre-existing calcinosis in JDM with pamidronate therapy has not been previously described with any of the aforementioned treatments. The advantage of treatment with pamidronate compared to treatment with alendronate is that intravenous administration does not produce esophagitis, the most frequent adverse event when orally administering bisphosphonates. Our results strongly suggest that therapy with intravenous pamidronate in conjunction with good disease control with DMARD therapy is an apparently safe and effective treatment for calcinosis management in JDM.

Key words

Calcinosis, pamidronate disodium, childhood type dermatomyositis, aredia.

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Introduction

Juvenile dermatomyositis (JDM) is a chronic muscular inflammatory disease of unknown aetiology with an annual incidence of between 0.29 and 0.34 per 100,000 children (1). The average age of onset is 7 years, and the disease is more frequent in girls with a female-to-male ratio of 2.7:1 (1). The presence of a pathognomonic rash and three of the other four following criteria are required for a definite diagnosis of JDM: symmetric proximal muscle weakness, electromyographic evidence of inflammatory myopathy, elevated serum muscle enzymes (CPK, GOT, LDH, aldolase) and inflammatory myositis on a muscle biopsy; the presence of a pathognomonic rash and two of the cited four criteria are required for a probable diagnosis of JDM (2). JDM affects not only skeletal muscles: visceral vasculitis, widespread nervous system vasculitis and cardiopulmonary disease may also be found.

Calcinosis is a frequent finding in up to 40% of children with juvenile dermatomyositis which may occur in muscles, skin, subcutaneous tissue and fascial planes (1). Dystrophic calcifications usually develop late in the evolution of the disease, but can sometimes develop earlier and usually affect legs, thighs, elbows, knees or fingers. Although the nucleus consists of hydroxyapatite, other minerals (calcium oxalate and uric acid) and macrophages (IL-6, IL-1 and TNF-alpha) may also be present (1, 3). Calcium deposition around the joints can cause joint contracture and long-term disability.

Different treatments (aluminum hydroxide, diltiazem, probenecid, alendronate, etc.) have been used in an attempt to clear calcinosis and to avoid the onset of new calcium deposition, but none has proved clearly effective.

Bisphosphonates are chemical analogues of pyrophosphates which have been developed in the two last decades and have powerful effects on bone metabolism. Bisphosphonates are mainly applied clinically as inhibitors of bone resorption in bone diseases in which excessive osteoclast activity is an important pathologic feature of osteoporosis or osteogenesis imperfecta (4, 5).

Pamidronate is a nitrogen-containing bisphosphonate with a potent inhibiting bone resorption effect that has been used to treat osteoporosis in children (6). It lowers blood levels of calcium, inhibits bone resorption which causes diminished bone calcium mobilisation and also destroys macrophages by lowering the pro-inflammatory cytokines (IL-1 β , IL-6 and TNF-alpha) that they release (3).

We report three children with JDM who developed calcinosis and received intravenous Pamidronate with good results. Indeed, calcinosis completely cleared in one of the three patients.

Patients and methods

All three patients met the Bohan and Peter diagnostic criteria for JDM (2). Clinical and analytical data were collected retrospectively. The presence and evolution of calcinosis was assessed with sequential x-rays. The laboratory measures used to document muscle disease activity were CPK, LDH, GOT and aldolase; ESR was used to measure systemic activity. Any adverse effects occurring during the treatment period were also noted. Bone density at the lumbar spine L2-L4 was quantified by dual energy x-ray absorptiometry (DXA) prior to and one year after beginning treatment. Vertebral area bone mineral density (BMD, g/cm²) and Z-score (comparison between the BMD in a patient and the average BMD value in a population of similar gender and age) were calculated. The normal values for bone mineral density in children are summarised in the tables of the work by Carrascosa *et al.* (7). Osteoporosis, osteopenia and normal bone mineral density are defined by a z-score of ≤ -2 , between -1 and -2, and > -1 (8, 9), respectively.

All three patients had undergone physical therapy once a week for one year before starting pamidronate treatment. Intravenous pamidronate was given at 1 mg/kg/day on three consecutive days every three months according to the protocol established by Glorieux *et al.* for osteoporosis treatment in osteogenesis imperfecta (10). The mean duration of the disease in our patients prior to pamidronate therapy was three years.

The drug was obtained for the three

Competing interests: none declared.

Table I. Clinical data.

	Patient 1	Patient 2	Patient 3
Gender	Male	Female	Male
Age at diagnosis	7 years	3 years	8 years
Disease duration	4 years	3 years	2 years
Treatment	- Prednisone 1-2mg/kg/day (June 2002–June 2005) - Methotrexate (MTX) 0.35 mg/kg/week PO (July 2005) - Hydroxychloroquine (HCQ) 3mg/kg/day (November 2005) - Pamidronate 1 mg/kg/day, 3 consecutive days every 3 months (June 2005–August 2007).	- Prednisone 0.3mg/kg/day (September 2001–April 2005) - MTX 0.35 mg/kg/week PO (December 2004) - Tacrolimus 0.075mg/kg/day (December 2005) - Diltiazem (September 2001–April 2005) - Pamidronate 1 mg/kg/day 3 consecutive days every 3 months (April 2005–August 2008), and then every 6 months	- Prednisone 1-2 mg/kg/day (September 2003–April 2004) - Gammaglobuline 2gr/kg/day; 2 consecutive days each month, for the first six months (November 2003–April 2004) - Cyclosporine 3 mg/kg/day (November 2003–December 2004) - Tacrolimus 0,075mg/kg/day (December 2004) - MTX 0.35 mg/kg/week s.c. (November 2003–April 2004). - MTX 0.35 mg/kg/week PO (April 2004–December 2004) - MTX 0,35 mg/kg/week s.c. (December 2004) - Hydroxychloroquine 3mg/kg/day (November 2003) - Pamidronate 1 mg/kg/day 3 consecutive days every 3 months (November 2005–November 2007), and then every 6 months
Location of calcinosis	Right arm and right gluteus	Right arm and right tensor of fasciae lata	Right gluteus and right tensor of fasciae lata

Table II. Analytical parameters before and after one year of pamidronate therapy.

	VSG Pre (mm/h)	VSG Post (mm/h)	CPK Pre (UI/L)	CPK Post (UI/L)	LDH Pre (UI/L)	LDH Post (UI/L)	GOT Pre (UI/L)	GOT Post (UI/L)	Aldolase Pre (UI/L)	Aldolase Post (UI/L)
Patient 1	13	9	50	111	450	431	25	39	5	5
Patient 2	4	8	78	16	789	449	35	25	32	9
Patient 3	15	8	112	172	1074	663	39	50	20	10

patients for compassionate use after receiving their parents' written informed consent.

Results

The clinical characteristics of the three patients are summarised in Table I and their analytical evolution is shown in Table II. There were no significant changes in phosphorus and calcium levels after pamidronate therapy. We observed an improvement in bone mineral density after pamidronate therapy in all three patients. Only one adverse reaction to treatment shortly after the first administration of pamidronate was reported for patient 1, who was feverish and had backache. Symptoms were controlled with standard doses of acetaminophen and did not recur during subsequent treatment cycles. Calcinosis completely

cleared in patient 1, while the other 2 patients are still receiving pamidronate.

Patient 1

An 11-year-old boy from Morocco, who had been diagnosed with JDM at the age of 7, had proximal muscular weakness, myalgias, arthralgias, weight loss, heliotrope and Gottron's papules. He developed calcinosis in his right arm and right gluteum during the first three years of disease. In Morocco and from the time of his diagnosis, he received prednisone at a dose of 1-2 mg/kg/day for 3 years. When he moved to Spain and was transferred to our centre, a biopsy of the dystrophic calcification was done to confirm the diagnosis as the radiological image was not definitive for calcinosis. Once a definite diagnosis had been confirmed, intravenous pa-

midronate commenced at 1 mg/kg/day on three consecutive days every three months. One month and five months later, respectively, oral methotrexate at 0.35 mg/kg/week and hydroxychloroquine at 3 mg/kg/day were associated because of the persistent inflammatory activity noted with good clinical results, and prednisone was discontinued. After the patient had received 10 courses of pamidronate, his calcinosis had completely cleared (Fig. 1) and the therapy was discontinued. Bone mineral density improved after pamidronate therapy (previous BMD 0.475 g/cm² and posterior BMD 0.736 g/cm²; previous z-score -0.97 and posterior z-score 0.23). One year later, the patient continues his treatment with methotrexate and hydroxychloroquine, he is still asymptomatic and calcinosis has not recurred.

Patient 2

A 6-year-old girl, who had been diagnosed with JDM at the age of 3, had muscular weakness, difficulty in walking, heliotrope and Gottron's papules. Calcinosis in the biceps, triceps, and right tensor of fascia lata developed when the first symptoms of the disease appeared. Prednisone at 0.3 mg/kg/day, oral methotrexate at 0.35 mg/kg/week and tacrolimus at 0.075 mg/kg/day were introduced with good clinical and analytical responses. Her previous therapy included diltiazem, but calcinosis was not resolved and even increased. Four months later, intravenous pamidronate was introduced at 1 mg/kg/day on three consecutive days every three months. After 11 courses, calcifications had decreased (Fig. 2), pain had resolved and no new calcinosis had appeared. Bone mineral density had also improved after pamidronate therapy (previous BMD 0.511 g/cm² and posterior BMD 0.598 g/cm²; previous z-score -0.3 and posterior z-score 0.78). Presently, the patient continues with a treatment of tacrolimus, methotrexate and pamidronate every six months.

Patient 3

A 10-year-old boy, who had been diagnosed with JDM at the age of 8, had systemic involvement, fever, muscular weakness, dysphagia, heliotrope and Gottron's papules. Calcinosis developed in the right gluteus and the right tensor of fasciae lata two years after diagnosis. He started a monthly treatment with intravenous methylprednisolone and gammaglobulin for the first six months because of the patient's systemic involvement. When the patient improved, methylprednisolone was discontinued and he began taking oral prednisone at 1-2 mg/kg/day and cyclosporine (CYP) at 3 mg/kg/day, oral methotrexate at 0.35 mg/kg/week, and hydroxychloroquine at 3 mg/kg/day was added. A year after therapy had begun, the disease continued to be active despite treatment with MTX, CYP and hydroxychloroquine (HCQ). Cyclosporine was discontinued and therapy with tacrolimus at 0.075 mg/kg/day began.

Pamidronate was introduced one year later at 1 mg/kg/day on three consecu-

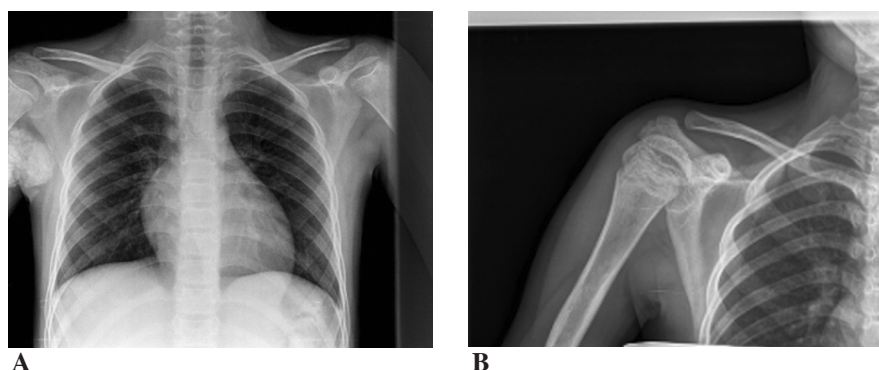


Fig. 1. Complete resolution of calcinosis after administration of pamidronate in patient 1. **A.** Right arm calcinosis before pamidronate therapy. **B.** Complete resolution after 10 courses of treatment.

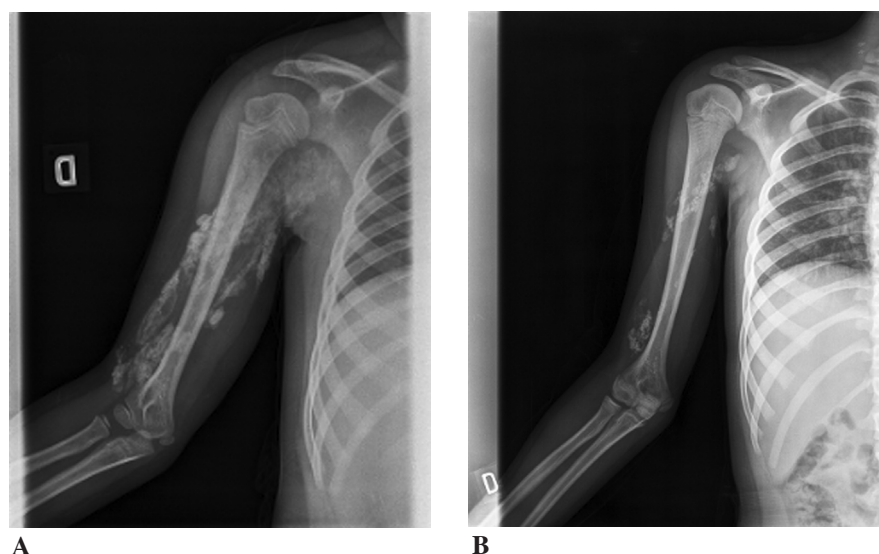


Fig. 2. Marked reduction of calcium deposition in patient 2. **A.** Right arm calcinosis before pamidronate therapy. **B.** Calcium deposition had markedly reduced after 11 courses of pamidronate.

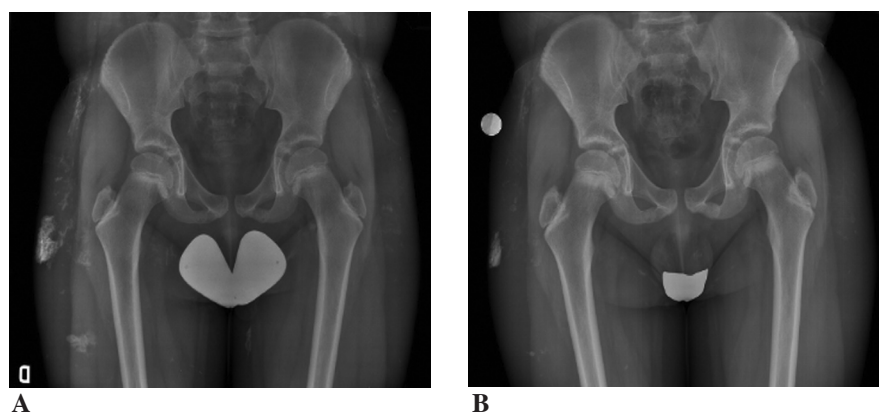


Fig. 3. Marked reduction of calcium deposition in patient 3. **A.** Right tensor of fasciae lata before pamidronate therapy. **B.** Calcium deposition had markedly reduced after 11 courses of pamidronate.

tive days every three months. After 11 courses of intravenous pamidronate, calcifications had decreased (Fig. 3) and no new calcinosis had appeared. Bone mineral density had improved after pamidronate therapy (previous BMD 0.68

g/cm² and posterior BMD 0.845 g/cm²; previous Z-score 0.4 and posterior z-score 0.92). Presently, the patient continues with a treatment of tacrolimus, methotrexate, hydroxychloroquine and pamidronate every six months.

Discussion

The pathogenesis of calcinosis is not completely understood. However, an increase of mitochondrial calcium liberation from damaged muscular cells due to the presence of muscular inflammation has been proposed to play a key role in the formation of calcinosis (11). There are some factors which contribute to the development of dystrophic calcifications which include the presence of chronic inflammation (a necessary condition for the generation of pathologic calcifications), some genetic factors, and environmental factors and clinical characteristics of the underlying disease (12). An inflammatory response leads to an increased release of chemokines and cytokines (TNF- α). This release is responsible for the formation of such calcifications, as some studies on milk calcium have shown the presence of macrophages and IL-1, IL-6 and TNF- α .

The initial use of corticosteroids and immunosuppressive therapy to stop inflammatory activity is one of the most important steps to prevent calcinosis formation (12-14). A relationship between the development of calcinosis in JDM and the presence of the A-308 polymorphism in the TNF- α gene has been demonstrated since this polymorphism has been associated with increased TNF- α production (12). Dystrophic calcification is more frequent in JDM than in adults with dermatomyositis. Indeed the highest prevalence of dystrophic calcification is observed in patients with more severe skin involvement and UVB sun exposure (12).

There is no universally recognised treatment for calcinosis and several drugs have provided poor results. In the 80s, aluminium hydroxide was used and some reports of improvement of calcinosis in JDM were published. Nevertheless, the effectiveness of this treatment was not demonstrated in later years (15-17).

Diltiazem is a drug with an inhibiting effect in the calcium channels of the cellular membrane. It is also used (at 360 mg/day) in adults with calcinosis secondary to dermatomyositis (DM) or systemic sclerosis, and offers a slight improvement in some DM cases, but not for systemic sclerosis (11).

Probenecid is a sulphonamide derivative that acts by increasing the urine phosphate excretion in the proximal renal tubule and lowering serum phosphorus (17). It has been used to treat calcinosis in some cases of JDM where increased serum phosphorus levels, secondary to increased tubular reabsorption, have been observed (17-19). However, this treatment was effective in only a few patients (20).

Very few studies on patients with JDM and calcinosis treated with bisphosphonates have been conducted. Pamidronate inhibits bone resorption by diminishing osteoblast apoptosis and by increasing osteoclast's apoptosis (21-23), leading to diminished bone calcium mobilisation and calcium deposition, and it destroys macrophages by lowering the pro-inflammatory cytokines (IL-1 β , IL-6 and TNF- α) that they release (3). This explains why bisphosphonates are effective in avoiding the formation of new calcinosis. However, the mechanism by which the treatment with bisphosphonates clears pre-existing calcifications remains unknown (3, 24).

Alendronate is an orally administered nitrogen-containing bisphosphonate with a high inhibition on the bone resorption action which has been used to treat calcinosis in JDM with good results (3, 24). The effectiveness of infliximab in JDM with calcinosis that is resistant to multiple treatments has been recently demonstrated in five patients. In some patients, an improvement of calcinosis has been attributed to a synergistic work done between infliximab and pamidronate that the patients were also receiving (25).

Our patients underwent therapy with pamidronate which was given intravenously with very good results since calcinosis significantly decreased in all three cases, and even completely cleared in patient 1.

Complete resolution of pre-existing calcinosis in JDM with pamidronate therapy has not been previously described with any of the aforementioned treatments. It is difficult to determine whether improvement in calcinosis is only due to pamidronate therapy or if the control of the inflammatory activity achieved with disease-modifying drugs

also plays a role. Nevertheless it has to be pointed out that before administering pamidronate, those patients with calcinosis due to JDM did not show the improvement that our patients did even when the disease was well controlled with modifying drugs. In patient 3, calcinosis appeared two years after diagnosis when he was already receiving s.c. MTX and Tacrolimus, and the disease was almost under control without further changes in the modifying drugs, which implies that pamidronate has played an important role in calcinosis improvement.

The advantage of pamidronate treatment compared to alendronate treatment is that intravenous administration does not produce esophagitis, the most frequent adverse event of orally administered bisphosphonates (24). In addition, its administration on three consecutive days every three months is much more convenient and allows greater therapeutic adherence than a daily oral administration pattern.

Our results suggest that intravenous pamidronate therapy in conjunction with good disease control with DMARD therapy is an apparently safe and effective treatment in the management of calcinosis in JDM. Further controlled clinical studies with a larger number of patients could be done to assess the results obtained in our group of patients.

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