Rapid Improvement of Calcinosis in Juvenile Dermatomyositis with Alendronate Therapy

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ABSTRACT. A 6-year-old boy with improving juvenile dermatomyositis (JDM) developed severe and debilitating calcinosis, unresponsive to diltiazem and probenecid. Alendronate produced dramatic improvement within 1 month and by 12 months calcinosis had virtually resolved. The response was followed by bone mineral content measurements. (J Rheumatol 2005;32:1837–9)

Key Indexing Terms: JUVENILE DERMATOMYOSITIS CALCINOSIS BISPHOSPHONATES

Calcinois is a frequently reported complication of juvenile dermatomyositis (JDM), occurring in 10%–50%. It can be painful and debilitating and result in major disability. The pathogenesis is incompletely understood, although it involves inflammatory cell cascades, cytokines, and mineralized matrix proteins following tissue injury and inflammation. Many therapies have been tried for calcinosis with variable success, including hydroxychloroquine, intravenous immunoglobulin, cyclosporine, infliximab, colchicine, local triamcinolone, probenecid, diltiazem, and aluminum hydroxide.

Recently, there have been 2 reports of successful treatment with bisphosphonates, one in combination with diltiazem. We describe a dramatic improvement in a patient with severe calcinosis with alendronate therapy.

CASE REPORT

An 8-year-old boy had JDM diagnosed at age 3.25 years after 3 months of increasing lethargy, muscle pain, rash, and weakness. Clinical and laboratory features supported the diagnosis of JDM, with overlap syndrome considered unlikely, although myositis-specific and myositis-associated antibodies were not tested. He improved with prednisone, but did not achieve adequate remission, and methotrexate (MTX) was added one year later. Early subcutaneous calcification (buttocks and abdomen) occurred, which steadily increased and spread. Probenecid was added (500 mg twice daily) and then diltiazem (15 mg twice daily). By the age of 6.2 years, he was felt to be in remission from the JDM, with resolution of rash, normal proximal muscle strength, and normalization of previously elevated creatine kinase, alanine transaminase, and aldolase. However, the calcinosis rapidly worsened over the chest and abdominal walls (Figure 1), arms, thighs, and buttocks. Knee and elbow flexion were markedly reduced and the subcutaneous calcification resembled an exoskeleton. Muscle strength remained normal apart from some mild distal weakness (by clinical examination, Medical Research Council scale 4+/5), which was thought to be related to the location and severity of the calcinosis. Episodes of inflammation, breakdown, and suppuration of calcinotic lesions occurred and he required several surgical drainage procedures, courses of intravenous and oral antibiotics, and 4 weeks of hospitalization. Quality of life was poor with pain and worsening immobility. Total and regional bone mineral density (BMD) and bone mineral content (BMC) by dual-energy x-ray absorptiometry (DEXA; Lunar Prodigy, GE Lunar Corp., Madison, WI, USA; software 6.10.029) were normal for age (BMD age z-scores: total +0.09, lumbar spine +0.32; BMC age z-scores: total +1.79, lumbar spine +1.53), although they were possibly confounded by extraskeletal calcification.

Alendronate 10 mg daily (0.4 mg/kg or 10.9 mg/m²) was started. Prednisone (20 mg/5 mg alternating daily, averaging 0.5 mg/kg/day) and MTX (15 mg weekly, 0.6 mg/kg weekly with folic acid supplements) were continued. Probenecid and diltiazem were stopped. Within one month there was dramatic improvement in symptoms with softening of calcinosis, ces-
sation of extrusion, and marked increase in joint mobility, for example, left elbow flexion increased from 18° to 80°. After 12 months of alendronate treatment he had almost complete resolution of calcinosis, the only residual problem being right Achilles tendon nodules and a loculated, liquefied collection in the right calf that was successfully drained surgically with no recurrence. Prednisone was tapered and then stopped 13 months after alendronate was started. Alendronate was well tolerated with no adverse effects, including no esophagitis, and was stopped after 15 months. Six months later there has been no recurrence and MTX is currently being withdrawn.

Computer tomographic scan (lower limbs) over the period of treatment showed significant resolution of the extensive calcification of the subcutaneous plane, muscles, and intermuscular planes. On DEXA, reduction in calcinosis was evident on the visual images (Figure 2). While total BMC and BMD had increased with growth and 9 months of alendronate treatment, regional BMC values (Table 1) were significantly reduced in the areas that had been most affected by calcinosis, presumably reflecting the reduction in soft tissue mineral content.

DISCUSSION

The best approach to treating calcinosis associated with JDM remains unclear. The difficulties are compounded by its rarity and the variable and unpredictable natural history. Calcinosis is reported to be more likely in those with delay in diagnosis and therapy of JDM, inadequate initial therapy, and chronic disease, and is more likely to progress when there is ongoing disease activity. More severe forms of calcinosis (including exoskeleton) seem less likely to respond or resolve spontaneously. The extensive list of attempted therapeutic agents reflects that efficacy is suboptimal and variable.

Our patient developed severe and worsening calcinosis, despite adequate therapy with prednisone and MTX and marked improvement of his underlying JDM. Probenecid alone and in combination with diltiazem was unsuccessful. These agents have been reported to have efficacy in a small number of subjects with calcinosis of a variety of causes. There are only 2 reports of the use of bisphosphonates in the treatment of calcinosis in JDM. Mukamel, et al reported rapid improvement with alendronate (oral 10 mg/day) in a 6-year-old boy with a history very similar to our patient with near complete resolution of calcinosis by one year. However, their patient had severe osteoporosis, in contrast to our patient with normal BMD. Oliveri, et al reported

![Figure 2. DEXA studies (total body and left hip) before (left) and after 9 months of alendronate therapy.](https://www.jrheum.org)

<table>
<thead>
<tr>
<th>Standardized Region</th>
<th>BMC, g, Pre-Alendronate</th>
<th>9 mo Alendronate</th>
<th>Change in BMC, g (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right femoral neck</td>
<td>1.57</td>
<td>1.42</td>
<td>-0.15 (-9.6)</td>
</tr>
<tr>
<td>Right proximal femur</td>
<td>19.67</td>
<td>11.15</td>
<td>-8.52 (-43)</td>
</tr>
<tr>
<td>Left femoral neck</td>
<td>1.79</td>
<td>1.64</td>
<td>-0.15 (-8.4)</td>
</tr>
<tr>
<td>Left proximal femur</td>
<td>27.80</td>
<td>11.96</td>
<td>-15.84 (-57)</td>
</tr>
<tr>
<td>Arms</td>
<td>145.2</td>
<td>90.4</td>
<td>-54.8 (-38)</td>
</tr>
<tr>
<td>Spine L2–L4</td>
<td>17.34</td>
<td>19.76</td>
<td>+2.42 (+14)</td>
</tr>
<tr>
<td>z-score +1.53</td>
<td>z-score +1.76</td>
<td>+82.49 (+8.8)</td>
<td></td>
</tr>
<tr>
<td>Total BMC</td>
<td>937</td>
<td>1020</td>
<td>+82.49 (+8.8)</td>
</tr>
<tr>
<td>z-score +1.79</td>
<td>z-score +1.87</td>
<td></td>
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</tr>
</tbody>
</table>
similar regression in an 8-year-old girl with progressive calcinosis and exoskeleton treated with a combination of pamidronate (oral 4 mg/kg/day) and diltiazem, although the combination therapy does not allow the effective agent to be determined.

The mechanism of action of bisphosphonate in regression of calcinosis is unclear. Bisphosphonates are known to be potent inhibitors of osteoclast activity and for their efficacy in osteoporotic conditions. It has been proposed that they reduce calcinosis by reducing overall calcium turnover and inhibiting further calcium accretion to existing calcification. An inhibitory effect on macrophages has also been proposed. However, the effect may not apply to all bisphosphonates, since lack of efficacy of etidronate (a non-nitrogen-containing compound of lesser potency) has been reported in this situation.

Our report together with other case reports suggest a potential benefit of bisphosphonate therapy in dystrophic calcification associated with JDM; however, there are no reports of absolute efficacy and randomized controlled trials will be difficult to achieve. An empirical trial of therapy may be justified in difficult and deteriorating clinical situations.

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REFERENCES