Radiological features of bisphosphonate therapy in children with osteogenesis imperfecta

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Osteogenesis imperfecta (OI) is a genetic disorder of type-I collagen, which is one of the most prevalent osteoporotic syndromes in children. It is characterized by repeated fractures and skeletal deformities. No universal and effective medical therapy is available for this disorder. Many therapeutic agents have been tried without any convincing benefit. However, several recent clinical studies have reported beneficial effects of bisphosphonates in children with OI.[1,2] These studies showed that intravenous pamidronate improves symptoms of chronic bone pain, recurrent fractures rate, motor function and bone mineral density (BMD). The objective of this study is to determine and describe the radiographic features of cyclic pamidronate administration on the growing skeleton in children with OI.

We retrospectively reviewed the radiographs of 10 children (7 male, 3 female) treated with pamidronate. The age of these children ranged from 2-10 years. Pamidronate, which is an osteoclast inhibitor was administrated intravenously at 4 months intervals at the Pediatric Endocrinology Clinic, King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia for 2 years. The annual total dose was 9mg/kg/year. Radiographic frontal views of the hands, wrists, and knees were obtained every 6 months. Other radiographs obtained for clinical indications during the treatment and follow-up periods were also reviewed as part of this study. Lumbar and whole body BMD were assessed biannually. Bone mineral density determinations were performed using a Hologic QDR4500 dual-energy x-ray absorptiometer with pediatric scan and analysis functions. Z scores, the number of standard deviations (SD) for BMD above or below the mean for age-matched controls, were derived on the basis of the manufacturer's data.

Prior to treatment, baseline radiographs showed generalized osteopenia, bone bowing and fractures with fracture deformities. Post treatment, there were multiple sclerotic metaphyseal bands seen in all children in the long bones paralleling to the growth plates and corresponding to the number of treatment cycles (**Figure 1a & 1b**). The metaphyseal bands were seen as early as 3 months after the first treatment cycle and became more visible over time as the growth separated them from the zone of provisional calcification.

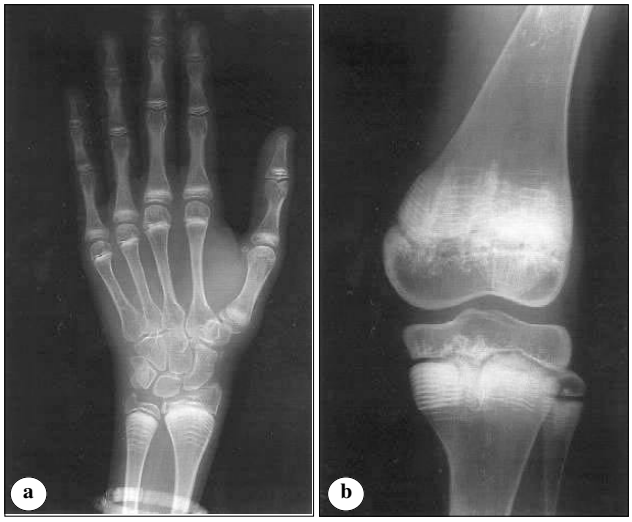

Figure 1 - Radiographs showing **a)** Multiple sclerotic metaphyseal bands are seen in the distal ends of the ulna and the radius, **b)** distal ends of the femur and proximal end of the tabia, which are parallel to the growth plates and correspond to the number of treatment cycle.

During the course of treatment, a gradual increase in bone density was observed in all patients. Before treatment, the mean lumbar BMDz score was -4 $\pm$ 1.3, which improved to a mean score of -3.1 $\pm$ 1.2 one year post treatment, to a mean score of -2.7 $\pm$ 1.1 at the end of therapy. The mean whole body BMDz score was -2$\pm$1.2 at the start of therapy. After one year of therapy, the mean whole body BMDz score was -1.7 $\pm$ 1.1. At the end of treatment, the whole body BMDz score was -1.1 $\pm$ 1.3.

There was a significant decrease in radiologically confirmed fracture rate from a mean of 4.2 $\pm$ 1.5 fractures per year pretreatment to a mean of 1.8 $\pm$ 1.2 fractures per year during the first year of treatment to a mean of 0.3 $\pm$ 0.1 fractures per year during the second year of treatment, All patients were fracture free during the last 6 months of therapy.

There was also increased mineralization observed on conventional x-ray in all patients. Several studies have reported beneficial effects of bisphosphonate treatment in children with OI. Devogelaer et al[3] in 1987 were the first to report decreased pain and fracture rate and improvement of long bones calcification in children with OI treated with

bisphosphonates. Bembi et al[4] first reported an increase in BMD in children with OI treated with pamidronate for a period ranging from 22-29 months. Astrom and Soderhall[1] reported a major improvement in well being, pain and daily activities using pamidronate over a 2-5 years treatment period. A relatively recent published data supporting the use of bisphosphonates in infants and children with OI is the work of Glorieux et al[2] who have treated children ranging in age from 3-16 years with pamidronate. In this report, all children had dramatic decrease in pain, decreased propensity to fractures and improved quality of life. All patients continued to have new fractures during the first and half year of therapy, however all of them were fracture free during the last 6 months of therapy. The occurrence of new fractures might be related to increased mobility and acquisition of activities that the children were previously unable to perform. The lumbar and whole BMD improved significantly in all children. Lumbar increased to 1.7 SD and the whole body BMD increased to 0.9 SD during the treatment period.

Grissom and Harcke[5] reviewed the radiographs of 32 patients treated with pamidronate. They showed that cyclic pamidronate administration resulted in metaphyseal bands, which varied in spacing according to the age of the patient, rate of growth, and the location of metaphysis. The spacing in younger patients who were growing more rapidly was wider than older patients. Also the spacing was wider where growth was more rapid.

All children had transient self-limited symptoms similar to flu symptoms, low-grade fever and decreased appetite, which resolved with symptomatic treatment.

In conclusion, intravenous pamidronate therapy improves symptoms of chronic bone pain, recurrent fractures rate, and BMD in children with OI. The radiological features of pamidronate therapy in children with OI including the increased BMD and the narrow metaphyseal bands are distinctive that might be related to skeletal growth factors.

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References

1. Astrom E, Soderhall S. Beneficial effect of bisphosphonate during five years of treatment of severe osteogenesis imperfecta. ***Acta Paediatr*** 1998; 87: 64-68.
2. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. ***N Engl J Med*** 1998; 339: 947-952.
3. Devogelaer JP, Malghem J, Maldague B, Nagant de Deuxchaisnes C. Radiological manifestations of bisphosphonate treatment with APD in a child suffering from osteogenesis imperfecta. ***Skeletal Radiol*** 1987; 16: 360-365.
4. Bembi B, Parma A, Bottega M, Ceschel S, Zanatta M, Martini C, et al. Intravenous pamidronate treatment in osteogenesis imperfecta. ***J Pediatr*** 1997; 131: 622-625.
5. Grissom LE, Harcke HT. Radiographic features of bisphosphonate therapy in pediatric patients. ***Pediatr Radiol*** 2003; 33: 226-229.