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Benefits of Pamidronate Treatment in Osteogenesis Imperfecta

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Abstract Osteogenesis imperfecta is a hereditary disorder of connective tissues characterised by low bone mass and bone fragility. Previous studies demonstrated that cyclical pamidronate therapy is effective in increasing bone density and improving clinical outcomes in children with osteogenesis imperfecta. We report our experience in treating two children with cyclical intravenous pamidronate infusion. The benefits and problems of the treatment are discussed.

Key words Osteogenesis imperfecta; Paediatric; Pamidronate treatment

Introduction

Osteogenesis imperfecta (OI) is a genetic disorder of synthesis of collagen. This results in low bone mass, fragile bones and recurrent fractures. The phenotype is heterogeneous and is currently classified into seven types. The classical types I-IV of Sillence classification[1] are associated with mutation of type 1 collagen gene while the genetic basis of the newly identified types V, VI and VII remains to be determined.[2,3] Children with more severe forms of OI have multiple fractures and progressive deformities thus affecting their quality of life.

The impairment in bone formation in OI shifted the balance towards bone resorption. The patients thus have thin bones with few trabeculae, thin cortices and high remodeling activity.[4] Bisphosphonates adversely affect the function of osteoclast and also cause osteoclast apoptosis.[5] Pamidronate belongs to the second generation bisphosphonate and is a potent inhibitor of bone resorption. Prior studies showed that cyclical intravenous pamidronate infusion have been used successfully in children with OI in reducing bone resorption and increasing bone mass and density. The pamidronate therapy contributes to improvement of the clinical course in this chronic disabling disease.[6-8]

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Case Reports

Case 1

This is an 18-year-old girl suffering from type III osteogenesis imperfecta. She had recurrent fracture of limbs since neonatal period and was an immigrant from China when she was 10-year-old. The fractures were managed by orthopaedic surgeons and rehabilitation programme by physiotherapist and occupational therapists were implemented. Yet she had significant short stature with standing height of 120 cm, skeletal deformities with pectus excavatum, kyphoscoliosis and bowing of long bones with unequal lower limb lengths. She had recurrent bone pain over rib cage. Walking was possible with aids or furniture support and she can cope with daily life activities but need wheelchair when being outdoor. She had blue sclerae but did not have dentinogenesis imperfecta and hearing was normal. The girl has normal puberty and the menstruation has been regular.

The father did not have fracture but the two paternal aunts had recurrent fractures and were short with height of about 130 cm. Both of them live in Mainland.

Radiographs of long bones showed thin cortices and osteopenia. Old fractures were well healed. Kyphoscoliosis of thoracic and lumbar spine and decreased height of vertebrae (Figure 1) with compression fractures were evident on spine X-rays.

Dual-energy X-ray absorptiometry (DEXA) using UK reference population was performed. The spine bone mineral density (BMD) was 0.464 g/cm^2 (Figure 2) and mean Z score (matched for age & weight) was -5.7. That of femoral neck was not performed because of presence of old fracture of upper femur.

After informed consent, the girl was treated with cyclical intravenous pamidronate at a dose of 3 mg per kg body weight per infusion cycle at four month interval from year 1999 at 14-year-old. Calcium intake was optimised to ensure provision of calcium 1,000 mg per day.

The treatment was associated with acute-phase febrile reaction with transient fever and chills in the first cycle but she remained afebrile in subsequent cycles. She also had transient lymphopenia with lymphocyte count of 0.4x10^9/L in first cycle. Serum calcium level and liver function test remained normal during the course of therapy. Hypercalciuria with urine calcium/creatinine ratio up to 1.5 mmol/mmol before the start of the treatment cycle was detected in the first two years and urine calcium excretion later returned to normal. Ultrasound of kidneys showed that there was no nephrocalcinosis.

DEXA and radiographs were performed every year in first three years and then every two years. BMD gradually increased (Figure 2) and the mean Z score rose to -4.1 in 2003. Vertical height of spinal vertebrae also increased (Figure 3) but there was no significant improvement in the degree of kyphoscoliosis. Bone pain decreased in intensity.

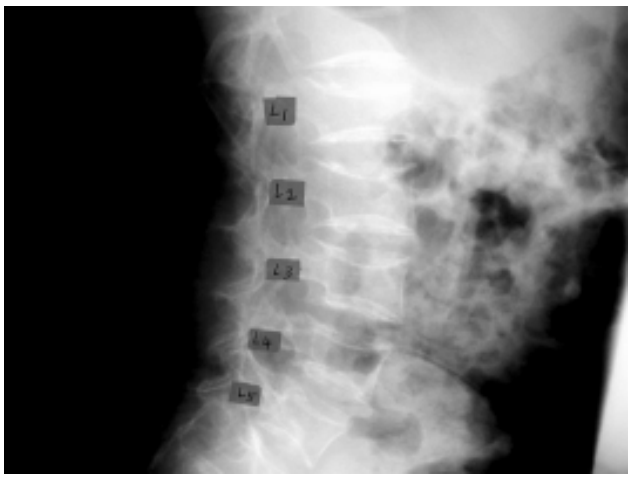

Figure 1 Lateral view of radiograph of spine of the girl (Case 1) before start of pamidronate treatment.

Case 2

This is an 13-year-old boy suffering from OI and the phenotype matched with that of type IV. He had recurrent fractures of limbs since three year old and had sustained about four fractures before he consulted us at about 11-year-old, averaging once fracture every two years. The standing height was on 3rd percentile (mid-parental height on 25th to 50th percentile) and he was in prepubertal stage. He did not have bone pain and was fully ambulant when he had no active fracture. Left hand function was impaired as a result of previous fracture of forearm. The boy did not have blue sclerae and the teeth and hearing were normal. Father had recurrent fractures in younger age but stature is normal.

X-rays showed osteopenia of long bones with healed fractures. Spine X-rays revealed decreased height of vertebrae with multiple compression fractures (Figure 4) and mild kyphosis of thoracic and lumbar spine. DEXA

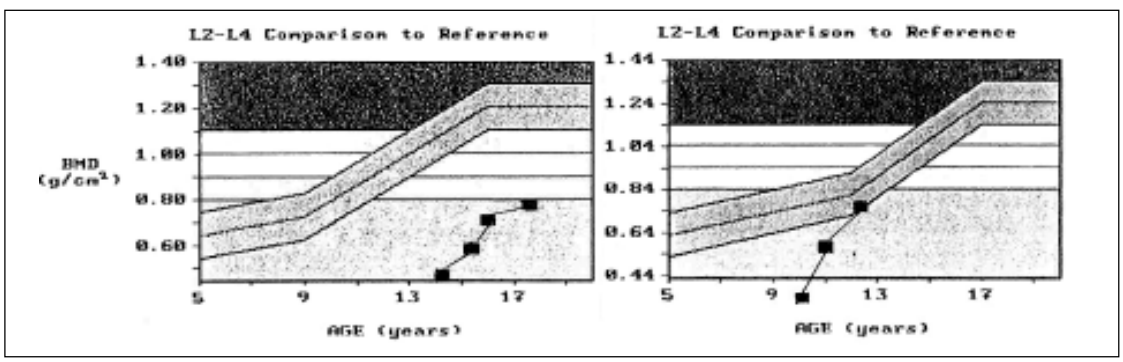

Figure 2 Changes in BMD of lumbar spine (L2-L4) in adolescent girl (Case 1) with type III (left) and boy (Case 2) with type IV (right) osteogenesis imperfecta treated with cyclic pamidronate. (Results plotted on the graph showing the range of BMD (±1 SD mean) in reference population of respective sex).

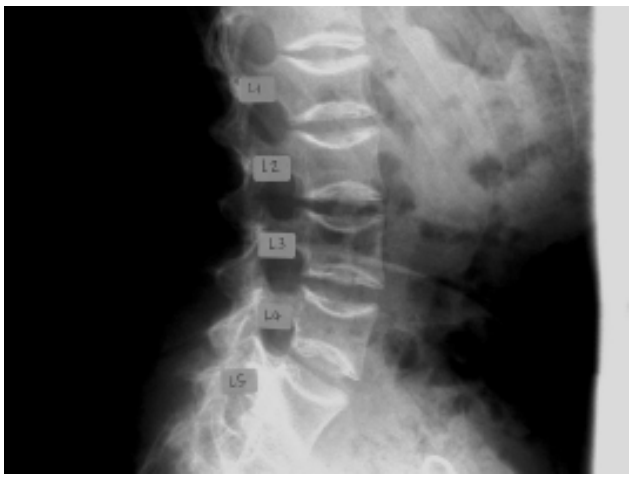

Figure 3 Lateral view of radiograph of spine of the girl (Case 1) after four years of pamidronate treatment showing increased vertebral height and improvement of compression fracture of vertebral bodies.

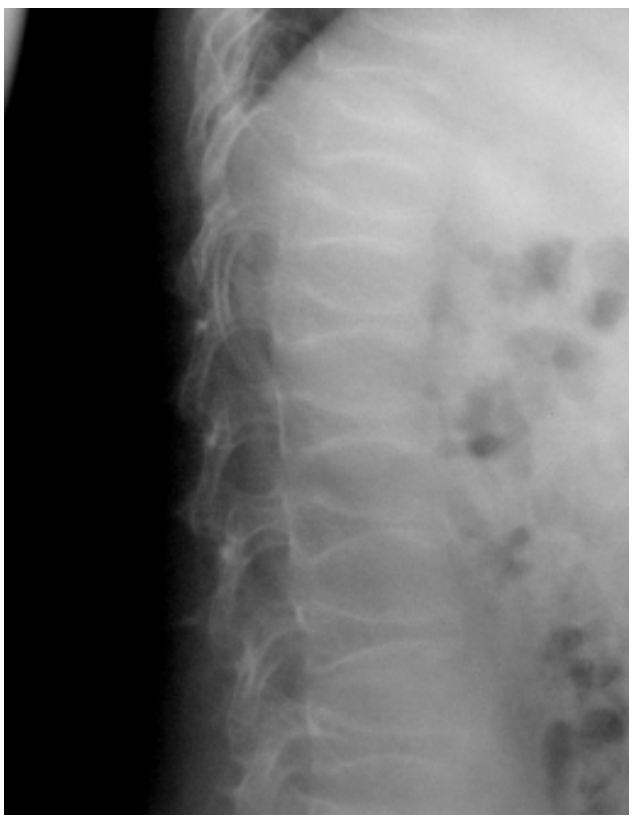

Figure 4 Lateral view of radiograph of spine of the boy (Case 2) before start of pamidronate treatment.

confirmed osteoporosis. The spine BMD was 0.323 g/cm^2 (Figure 2) and femur BMD was 0.46 g/cm^2. Mean Z score of lumbar spine was -3.9. Urinary excretion of bone resorption marker type I collagen N-telopeptide related to creatinine was grossly elevated to 697 nM BCE/mMC (Normal: <51).

In presence of recurrent limb fractures and extensive compression fracture of spinal vertebrae, he was managed with cyclical pamidronate infusion at dose of 0.75 mg per kg body weight per cycle at four month interval for two years.

There was no side-effect during the course of treatment. Mild hypercalciuria with urine calcium/creatinine ratio of 0.69 mmol/mmol was observed before the start of therapy but the urine calcium excretion remained normal since then. Renal ultrasound was normal.

After two years of pamidronate treatment, radiographs showed significant improvement in height of spine vertebrae and compression fracture of thoracic and lumbar spine (Figure 5). The thoracic kyphosis decreased from 33° before

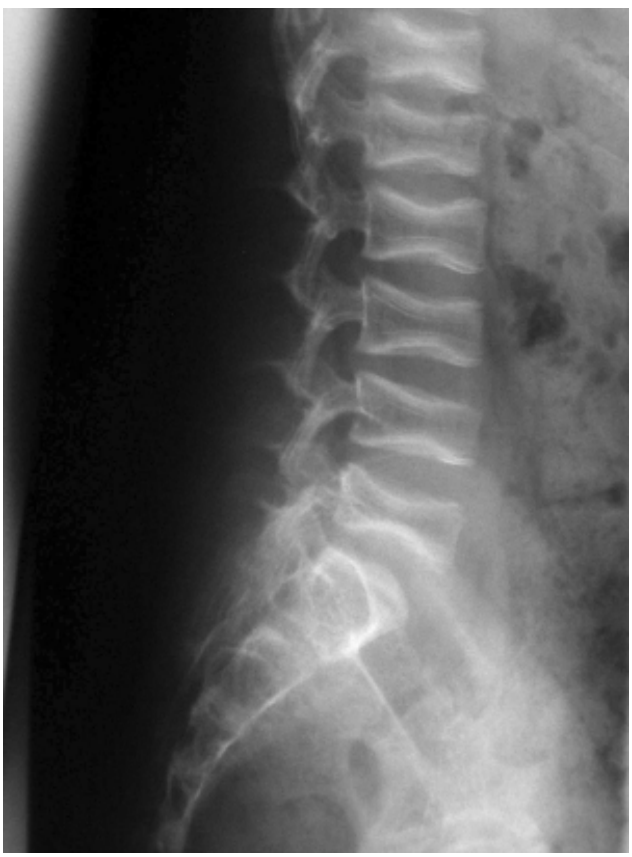

Figure 5 Lateral view of radiograph of spine of the boy (Case 2) after two years of pamidronate treatment showing increased height and improvement of compression fracture of vertebral bodies.

treatment to 15°. Long bones X-rays showed presence of sclerotic lines at metaphysis of distal radius and ulnar representing areas of increased bone density that are likely produced by cycles of pamidronate infusion (Figure 6). BMD increased dramatically. The spine BMD reached the normal range for age of 0.744 g/cm^2 (Figure 2) while femur BMD rose to 0.699 g/cm^2. The mean Z score was -0.5 at the end of two years. No new fracture was observed during the two years of pamidronate therapy. The standing height of the boy was in 3rd to 10th percentile and in stage III puberty. The pamidronate treatment was then stopped.

Discussion

The two case studies have demonstrated the beneficial effects of pamidronate therapy in improving bone density. This further supports the previous findings on positive effect of pamidronate treatment on the disease.[6-8] Classification of the type of OI in the two patients is based on the phenotype. The adolescent girl belongs to the more severe form of type III OI while the boy suffers from type IV OI which is a milder form of disease but had extensive spinal compression fractures. The girl had subjective decrease of bone pain. Both patients did not have new fracture during the treatment period. However we could not comment on the effect on limb fracture rate as the frequency of fractures in the girl already decreased after she entered late puberty while the observation period for the boy was only two years. The improvement in BMD is dramatic in both cases and vertebral remodeling was more significant in the boy with milder disease. His improvement in vertebral compression fractures and degree of severity of kyphosis might account for the good height velocity of about seven cm per year during course of treatment, though the previous growth data were not available.

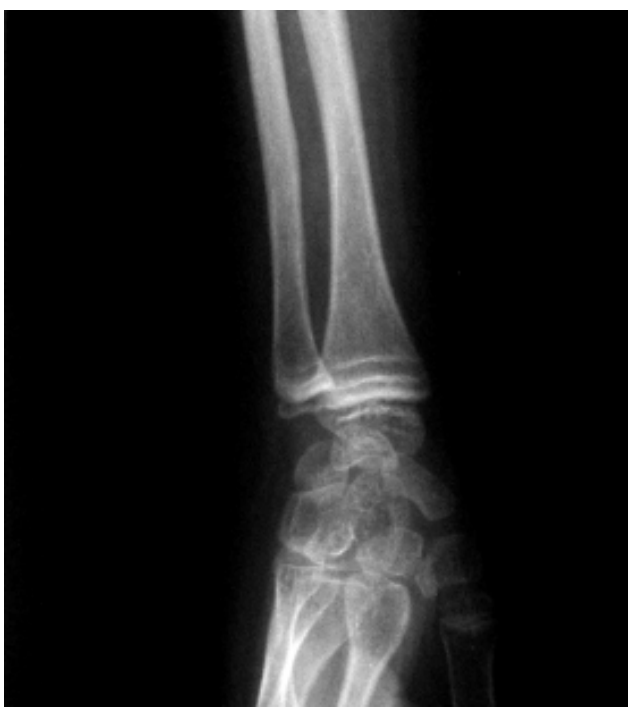

Figure 6 Radiograph of distal radius and ulnar of the boy (Case 2) showing the sclerotic growth lines after one year of cyclical pamidronate treatment.

Interpretation of lumbar BMD in patients with collapsed vertebrae may not be an accurate assessment of bone mass as the volume of the bone is not measured. However the improvement in vertebral height and size of vertebrae from new bone formation lead to underestimation of the increase in bone density and hence the therapeutic effect. The significant short stature of the girl also affect assessment of Z score as this is compared to the age-matched controls. On the whole, both parameters are good indicators in monitoring the response to treatment.

Hypercalciuria was observed in the girl during the first two years of pamidronate treatment. This is unlikely to be due to excessive dietary intake as advice was offered by dietitian and the mobility did not change. She had revision of metal rod over the old femur fracture in 2002 but urine calcium excretion already came back to normal at that time. The boy had mild hypercalciuria just before the start of course of treatment and then returned to normal. This could be explained by the reduced physical activity after fracture of left leg three months ago. The occurrence of hypercalciuria in the girl with more severe disease and its normalisation after two years of treatment when BMD improves might support the observation that magnitude of hypercalciuria in OI probably reflects the severity of the skeletal disease.[9]

No significant adverse effect from the therapy was observed. The problem that the girl had was transient acute-phase febrile reaction in first cycle and was readily controlled with antipyretic. Transient lymophopenia in the first cycle had no clinical sequaelae.

As pamidronate is depicted in bone and is detected years after treatment, the long-term safety and effectiveness of the drug in management of OI is not established yet. Hence it is important to consider treatment only in those with moderate or severe disease[6] or those with milder disease but have spinal compression fractures.[7] Introduction of oral form of bisphosphonates in management of OI in children

provide a convenient form of treatment.[10,11] However the dose and side-effects remain to be determined.

There is as yet no recommendation on the duration of pamidronate treatment. As the BMD of the boy reached normal range after two years, we decided to stop the treatment. Further monitoring of the BMD and fracture rate allow us to assess the preserved effect of the pamidronate therapy.

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