Intravenous Pamidronate Treatment in Filipino Children with Moderate to Severe Osteogenesis Imperfecta

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ABSTRACT

Objective. To present preliminary data on the effects of intravenous pamidronate in children with moderate to severe Osteogenesis Imperfecta (OI).

Methods. This is a retrospective study wherein a review of medical records and available serial radiographs of children (N=14) with moderate to severe OI started on pamidronate from 2006 to 2010 was done.

Results. Two children have OI Type I, 8 have OI Type III and 4 have OI Type IV. At baseline, 2 had normal height, 8 had height <-2SD and the rest with <-1SD. Twelve out of 14 had vertebral compression fractures. Mean age at start of pamidronate was 5.4 years (range 0.5- 11 years). First infusion fever in five patients and transient generalized macular rash in one child were noted. Serum calcium and phosphorus levels were normal at baseline and remained stable. Based on parental report, improvement of motor function was noted. In the 10 children who had at least a year of treatment, long bone fractures decreased from a mean annualized fracture rate of 2.6 at baseline to 0.9. In patients with vertebral compression fractures, serial radiographs showed improvement of vertebral shape.

Conclusion. This preliminary study shows that treatment was generally well tolerated and led to decrease in long bone fractures, improved vertebral shape and improved function.

Key Words: Osteogenesis Imperfecta, bisphosphonate, primary osteoporosis

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Introduction

Osteogenesis Imperfecta (OI) encompasses a group of clinically, radiographically and genetically heterogenous disorders of connective tissue caused in the majority by quantitative or structural deficits of type I collagen, leading to increased bone fragility.[1,2] This heritable metabolic disease has an overall incidence of 1:10,000 live births and has wide variability in the presentation and severity of the features.[3,4] Most affected individuals present with low trauma fractures, with associated extra-skeletal manifestations such as blue sclerae, dentinogenesis imperfect/opalescent dentin, hyperlaxity of ligaments and, and in older age group, hearing impairment.[3,5] Radiographically, OI may present with bowing of long bones, osteopenia or thin cortices with or without Wormian bones on skull x-ray.[1,5]

Historically, four major types were defined based on the classification by Sillence et al.[6] More recently, other types were added as bone histomorphometry and sequence analysis of genes have been more widely available. From the original four groups, OI classification has expanded to twelve distinct types each corresponding with a specific gene mutation wherein there is a range of phenotypic expression. These new types of OI are nearly all disorders resulting from autosomal recessive inheritance of mutations in genes regulating post-translational modification or trafficking of type I collagens. The Committee for the 2010 Nosology and Classification of Genetic Disorders of the Skeleton recommended 5 phenotypic and genetic descriptors and sub-classification of this condition (Table 1).[7] Non-deforming OI with blue sclerae - Type I, is the most common disorder and is usually mild in severity. The perinatally lethal form - Type II, is the most severe and infants with this usually succumb in the early months of life but a proportion of infants have very few rib fractures and these babies may survive to adult life. Progressively deforming OI - Type III, presents with severe bone fragility before birth or in the first year of life and there is progressive skeletal deformity. Variable OI with normal sclerae - Type IV is a common disorder with wide variability in manifestations ranging from mild to severe bone fragility and typically with white sclerae. OI with calcification of the inter-osseous membranes

and predisposition to hypertrophic callus formation, OI Type V, may be found in 10-15% of patients with moderate to severe disease. Other forms of OI are known but are rare, having other organ system features aside from fragile bones like Osteoporosis-Pseudoglioma Syndrome – a severe form of OI with associated blindness and intellectual disability, Cole-Carpenter Syndrome - OI with craniosynostosis and ocular proptosis, Bruck Syndromes - OI with congenital joint contractures, OI/Ehlers-Danlos Syndrome - fragile bones and extreme ligamentous laxity.[8] As more genes are being discovered to be responsible for phenotypes resembling OI, the classification is seen to expand some more.

Table 1. New Osteogenesis Imperfecta Nosology

Syndrome Name	Equivalent Numerical Type	Mode of Inheritance
OI, non-deforming forms	Type I	Autosomal dominant
OI, perinatal lethal forms	Type II	Autosomal dominant or recessive
OI, progressively deforming forms	Type III	Autosomal dominant or recessive
OI, moderate forms	Type IV	Autosomal dominant
OI with calcification of the interosseous membranes and/or hypertrophic callus	Type V	Autosomal dominant

OI is a lifelong disease and currently has no cure. Management is directed toward preventing or controlling the symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength.[4,9] Most medical treatments tried in the past had been generally ineffective.[9] In the more recent years, however, intravenous bisphosphonate therapy, more popularly used for post menopausal osteoporosis and as adjunct treatment for metastatic cancer, has been shown to improve bone mineral density and decrease fracture rates in children with OI. [10-12]

Biphosphonates are agents that interfere with bone resorption by inhibiting osteoclast activity, thereby decreasing bone turnover and increasing bone mineral content.[13] This group of drugs has been used to treat OI in the developed countries for more than two decades and studies have shown that aside from decreasing fracture frequency, bisphosphonates decrease bone pain and increase muscle strength.[10-12,14,15] Along with physiotherapy, it increases mobility and generally improves the activities of daily living.[14,15]

Pamidronate, like the other forms of bisphosphonates, have side effects that should caution physicians against indiscriminate use. An acute phase reaction, which would present typically during the first infusion, manifests as flu-like illness with varying severity of fever, nausea, vomiting and musculo-skeletal pains typically occurs in the majority of children. Hypocalcemia may also occur. More recently, osteonecrosis of the jaw after dental surgery or tooth extraction in adults on bisphosphonates has been reported. This has not been reported in children. Its pathogenesis is related to the total body accumulation of bisphosphonate and duration of therapy. It is recommended, therefore, that treatment with bisphosphonates is reserved to those with moderate to severe forms of OI.[4]

In 2006, the University of the Philippines-Philippine General Hospital Bisphosphonate Treatment Program for OI was started under the Clinical Genetics Service of the Department of Pediatrics. Pamidronate, an aminobisphosphonate was initially administered intravenously to a 6-year-old boy with OI Type III. Here, we report our experience in using pamidronate therapy in a small group of patients with moderate to severe OI from 2006 to 2010.

Methods

This is a retrospective study involving 14 prepubertal children, 7 males and 7 females, with moderate to severe OI on pamidronate therapy. These patients are classified to have moderate to severe OI having more than two long bone fractures in a year with or without vertebral compression fractures. In this study, the original Sillence classification was used basing the diagnosis on clinical manifestations and radiographs. This study aims to describe this group of children and to present preliminary data on the effects of treatment with pamidronate.

A review of medical records and available serial radiographs of patients with OI started on Pamidronate from 2006 to 2010 was done. Acquisition of patient data did not involve direct contact with patient and did not affect patient management. Eleven children received treatment in the Philippine General Hospital and three in private hospitals under the care of clinical geneticists following a modified treatment regimen based on the Bisphosphonate Treatment Program of the Connective Tissue Dysplasia Service of the Children's Hospital at Westmead.[16] Prior to starting treatment, data on demographics, anthropometric measurements were gathered. Baseline functional or motor ability was based on parental and physician's report as written on the medical chart. Number of fractures during the year prior to start of treatment was noted. Annualized fracture rate was computed by the number of fractures over time period in years (e.g. 3 fractures in 1 year: 3 fractures/1 year =3 fractures).

All subjects underwent skeletal survey and renal ultrasound. All had baseline complete blood count, serum calcium, phosphorus, magnesium, alkaline phosphatase, blood urea nitrogen and creatinine. 25-hydroxy Vitamin D level was requested.

Treatment involved priming dose of 0.5mg/kg of pamidronate for the first infusion followed by monthly infusion of 1 mg/kg for the first six months then same dose given every other month for the next six months. Bimonthly infusion was continued to the next year after assessment of

response. Monitoring of treatment response was done every 6 months with blood chemistry and lateral spine radiographs.

Results

Out of the 14 subjects, two children had OI Type I, 8 had OI Type III and 4 had OI Type IV. Mean age of diagnosis of OI was 31 months (range 1-120 months). At baseline, the 2 with OI Type I had normal height for age, 8 had height <-2SD and the remaining 4 with <-1SD (Table 2). Seven were mobile at start of treatment, 5 were not walking due to deformities of the lower extremities and 2 who were started at 6 months had no head control, were not rolling over and only minimally moving their extremities. Indication for starting treatment in all except one patient was recurrent long bone fractures (> 2 fractures in a year). The remaining patient, who had OI Type I, had no long bone fractures but had vertebral compression fractures resulting to scoliosis and severe back pain. Before the start of treatment, 12 out of 14 had multiple vertebral compression fractures.

All children were prepubertal at start of pamidronate treatment. Mean age at start is 5.4 years (range 0.5- 11 years). In the first year, dose ranged from 6-9 mg/kg/year while in the second, dose ranged from 5-6 mg/kg/year. No adverse reaction was noted apart from first infusion fever in five patients and transient generalized macular rash in one child (43%). Baseline renal ultrasound, complete blood count, BUN and creatinine were normal in all patients. Serum calcium, magnesium and phosphorus levels were normal at baseline and remained stable throughout treatment. Only four children (Subjects 8, 11 12, 14) had baseline 25-hydroxy vitamin D level and results were low (<50nmol/L) in all four. Correction with vitamin D supplement was done prior to start of treatment.

Based on clinical records on follow-up, all children had improved general well-being and function as early as the first infusion as reported by parents. Subjects who were walking independently at start of treatment (Table 1) were reported to have increased stamina. Those who were not able to move at baseline were able to move by bottom-shuffling and tolerate sitting longer. Subjects 13 and 14 were reported to be moving more especially the arms and legs.

In the 10 children who had at least a year of treatment, long bone fractures decreased from a mean annualized fracture rate of 2.6 at baseline to 0.9 during the first year of treatment. In patients with vertebral compression fractures and had at least a year of treatment (N=10), serial radiographs show improvement of shape of the vertebrae (Figure 1).

Discussion

OI is a connective tissue disorder where vast majority of affected individuals have mutations in COL1A1 and COL1A2, the genes encoding the chains of type I collagen.[17] Type I collagen is the most abundant protein in the extracellular matrix and is found in bone, skin, blood vessels and sclerae among others.[17] The clinical heterogeneity apparent in OI phenotypes is a reflection of the underlying molecular heterogeneity.[3,7,8] Mutations that only affect the amount of synthesized procollagen chains, generally result in OI of relatively milder severity while mutations resulting to qualitative as well as quantitative collagen defects lead to the more severe phenotypes. Multi-exon deletions or insertions in the COL1A1 and COL1A2 genes that encode the chains of type I collagen generally result in the lethal phenotype.[2,17] The genetic defect responsible for OI type V is yet to be discovered but some 9 other genes have been well characterized and homozygous or doubly heterozygous mutations in these genes generally result in progressively deforming disease or perinatally lethal disease.[8] These autosomal recessive types of OI may be the most frequent cause of OI in certain populations such as Southern Africa.

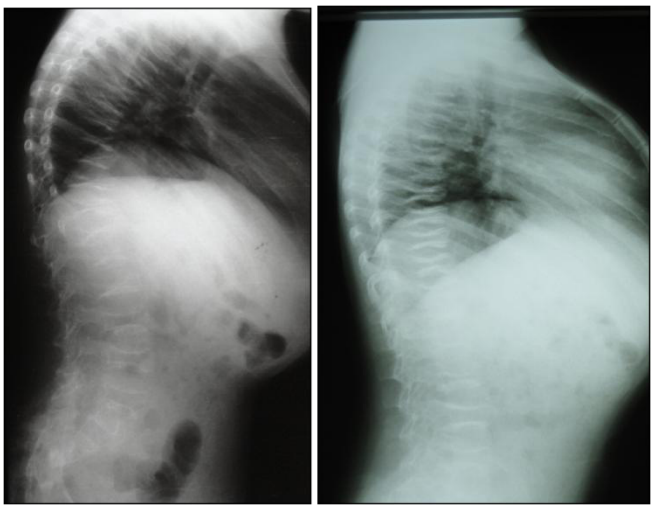

Figure 1. Lateral spine radiographs of a child with OI Type III before and after 1 year of treatment

Osteogenesis Imperfecta is a lifelong condition that requires lifelong management. At all ages, if left untreated, the poor quality of bone in OI leads to recurrent fractures and skeletal deformities. The consequent skeletal deformities and functional limitations are what concern the families and the care providers the most. These also make up the greatest burden in medical management. The treatment goal, therefore, is to improve bone strength in order to decrease frequency of fractures and minimize deformities.

The bone tissue is made up of osteoblasts (bone forming cells), osteoclasts (bone resorbing cells) and the osteocytes which maintain bone metabolism.[17] Continuous bone remodeling (formation and resorption) is needed to maintain the integrity of the skeleton and to make calcium available for instant mobilization for use of the body. Bone formation and resorption are coupled processes and tightly

Table 2. Baseline characteristics of subjects at start of treatment

Subject	Gender	OI Type	Age at Diagnosis (months)	Age at start of treatment (years)	Height SD	Weight SD	Vertebral compression fractures	Able to walk
1	Male	IV	84	6	<-2	<-1	Present	Yes
2	Male	III	72	8	<-2	<-2	Present	No
3	Female	III	24	9	<-2	<-2	Present	Yes
4	Female	IV	24	3.5	<-1	<-1	Present	Yes
5	Female	III	1	2	<-1	<-1	Present	Yes
6	Female	III	24	8	<-1	<-1	Present	Yes
7	Female	III	3	1	<-2	<-2	Present	No
8	Male	I	120	11	0	+1	Present	Yes
9	Male	III	1	10	<-2	<-1	Present	No
10	Male	III	3	8	<-2	<-2	Present	No
11	Female	I	12	6	0	0	Absent	Yes
12	Male	IV	18	1.5	<-1	<-1	Absent	No
13	Female	III	3	0.5	<-2	<-2	Present	N/A
14	Female	IV	3	0.5	<-2	<-2	Present	N/A

regulated.[13,17] Bisphosphonate is a group of drugs that inhibit the resorbtive action of osteoclasts.[13] Decreasing bone resorption would result to net bone formation with the use of bisphosphonates. Pamidronate, an aminobisphosphonate, has been used for children with moderate OI for two decades now. It has been shown to decrease bone pain, increase muscle strength, improve mobility, decrease fracture rate and increase bone density. In children started on pamidronate early, less than three years of age, it was shown to decrease fracture rate, increase BMD and improvement of vertebral shape and size.[14,15,18,19]

As seen in the previous studies, our preliminary results show decrease in fracture rate and improvement in vertebral shape. Moreover, in this study, parents report improvement in mobility, decrease in sweating and bone pain. Children with OI generally perspire more than normal which was formerly thought to be due to an increase in metabolism due to high bone turnover. A decrease in sweating during treatment might also be because of a decrease in micro-fracture rate.[12] Increase in mobility is most likely secondary to decrease in bone pain and the reported increase in muscle strength.[15]

Pamidronate therapy in our patients was generally well tolerated. Five experienced mild fever and one child developed transient generalized macular rash after the first infusion of pamidronate. These did not recur with succeeding infusions. Acute phase reaction which may manifest as "flu-like" symptoms such as fever, vomiting, body pains and malaise after the first infusion has been observed in other studies.[14,15,19] Hypocalcemia is another adverse event reported in bisphosphonate therapy. To minimize the risk of hypocalcemia, a normal baseline 25-hydroxy vitamin D should be assured before treatment is started. However, this test is expensive and is prohibitive to most of the subjects. To compensate for this lack of data in most of our patients, Vitamin D supplement was prescribed and taken by the children at least 2 weeks prior to start of treatment. Fortunately in this group of children, no hypocalcemia was noted.

Five out of 14 patients started therapy before three years of age. Most of these children started treatment already with varying degrees of bony deformities as well as vertebral compression defects. Studies have shown that early treatment may prevent and amend skeletal deformities, including spinal deformity.[12,14,15,19] Early diagnosis and referral for treatment would help in the improvement of functional capacity while minimizing the associated morbidity in OI.

Various pamidronate therapy protocols are being used world-wide. One of the more widely used is a cyclical infusion for 3 consecutive days with a 4-month interval is widely used.[12,14,15,18,19] In this study, the single day monthly infusion was used following the protocol developed in Europe[5] and in use at the Sydney Children's Hospital Network (Westmead campus)[16] which has also been found to be effective in other studies and may deliver a more physiologic correction of bone density.[12,20] In our setting where patients had to be admitted in wards shared with other patients with infectious diseases, this protocol allowed us to achieve efficacy without exposing the patients to increased risk of acquiring nosocomial infections associated with prolonged stay in the hospital. None of our patients developed any nosocomial infection while admitted for pamidronate infusion. Moreover, since pamidronate is an expensive drug and its price prohibitive to most of our patients, the monthly infusion provided a way for families to share a vial of the drug and hence, divide the cost.

Biphosphonate therapy in children with OI should be used alongside physiotherapy, occupational therapy, and surgery to correct skeletal deformities.[9,12] The improvement in mobility and reduction in pain with treatment permits more effective physiotherapy and increased activity. Surgical intervention with osteotomies and placement of intramedullary rods can lead to gains in bone length and earlier walking which stimulates new bone formation.[9,12]

Rod placement is recommended to control repeated fractures of a long bone, and to improve bone deformities that interfere with function.[21] The timing of surgery depends on the size of the bone which should have adequate diameter. Although children with moderately severe forms of OI have numerous fractures at birth, few new fractures occur until they start to stand and walk, hence surgery may be required at this time. Early involvement of other specialties like Orthopedics, Rehabilitation Medicine and Allied Medical Services would lead to a consolidated and holistic approach in the management of these children.

Conclusions and Recommendations

Pamidronate treatment in children with OI is relatively new in the Philippines. This preliminary study shows that treatment was generally well tolerated and led to decrease in long bone fractures and improvement in vertebral shape. Follow-up of this cohort through time is needed to be done to assess measurable effect in clinical outcome with use of uniform monitoring of parameters such as bone turnover markers, serial radiographs for vertebral morphometry and even bone densitometry. While other potent bisphosphonates have been investigated, the consensus worldwide is that the cyclic administration of Pamidronate is safe and is the treatment of choice in improving the quality of life in children with OI.

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