Change in Bone Mineral Density of Filipino Patients with Osteogenesis Imperfecta after 6 Months of Pamidronate Therapy in a Tertiary Hospital in the Philippines

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ABSTRACT

Background. Osteogenesis imperfecta is a heritable disorder due to a collagen gene mutation causing a structural abnormality leading to brittle bones and osteopenia. To address the osteopenia, intravenous bisphosphonates (pamidronate) act by temporarily halting the action of osteoclasts giving time for osteoblasts to build bone. To date, there has been no local data regarding the improvement in bone mineral density of Filipino patients with osteogenesis imperfecta following treatment.

Methods. This study is a retrospective review that included six patients aged 1 year and 10 months-9 years and 9 months old at the Philippine General Hospital with moderate to severe osteogenesis imperfecta who have undergone six months of pamidronate infusions at 1mg/kg/dose monthly or a total dose of 6mg/kg. Chart review was done. Hand radiographs taken at baseline and after six months of therapy were reviewed by a radiologist who was blinded, to determine metacarpal indices.

Results. There was an increasing trend in the metacarpal index from baseline to six months post-treatment with a mean difference of 0.053mm (CI -0.0112 to 0.117). However, the increase was not statistically significant (p value 0.0874) when analyzed using the paired t-test at a 95% confidence interval. No adverse events were noted and only one patient reported a fracture after starting therapy.

Conclusion. Bisphosphonate infusions among the six pediatric patients with moderate to severe osteogenesis imperfecta are well tolerated and although the increase in the metacarpal index from baseline after six months of treatment is not statistically significant, the trend shows improvement of the osteopenia from baseline.

Key Words: osteogenesis imperfecta, bisphosphonate, bone mineral density

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Introduction

Osteogenesis imperfecta (OI) or "brittle bone disease" is a heritable disorder caused by a mutation in the genes that code for pro-collagen, COL1A1 and COL1A2,[1] which leads to an increase in osteoclastic activity and a reduction in formation of new bone, and is reflected as decrease in bone mass.[1,2] To date, there are fifteen types of OI that have been identified according to clinical features and inheritance pattern.[3] The widely used classification is that of Sillence and colleagues.[4] Regardless of type, the clinical expression is primarily that of osteopenia, bone fragility, frequent fractures, progressive deformity, loss of mobility, and chronic bone pain.[1,5]

OI is the most common genetic cause of osteoporosis.[6] The prevalence is reported at 6-7 per 100,000.[7] According to the data available from the Philippine Osteogenesis Imperfecta Support Group, as of December 2014 there are 56 diagnosed patients in Luzon and 11 in the Visayas area. Since there is an absence of a formal national registry for OI, the true prevalence in the Philippines may be underestimated.

Based on the database of the Section of Genetics, Department of Pediatrics at the University of the Philippines-Philippine General Hospital (UP-PGH), there are 68 clinically diagnosed patients as of December 2014. However, only 41 are on regular follow-up. Of these 41, 6 have OI type 1, 18 have type III, 11 have type IV, and 6 have type V.

The definitive treatment for OI is gene therapy. Investigations are underway to the applicability of this therapy in humans. Medications seek to address the osteopenia that is present in osteogenesis imperfecta patients. The goal is to increase bone strength, either by increasing the amount of bone protein matrix or by increasing bone mineralization via a reduction in bone remodelling.[8]

Bisphosphonates are structural analogues of inorganic pyrophosphate. By specifically inhibiting osteoclast mediated bone-resorption, it presumptively allows bone-forming osteoblasts more time to promote bone formation,

albeit in the setting of abnormal collagen matrix as seen in patients with OI.[9,10] The use of intravenous pamidronate therapy has been widely studied in patients with OI and is noted to reduce the incidence of fracture and increase bone mineral density, while reducing pain and increasing energy levels.[1,2,8,11-17]

A study by Alcausin et al[18] reported that among 14 Filipino children with moderate to severe OI receiving intravenous pamidronate therapy, treatment was generally well tolerated and led to decrease in long bone fractures and improvement in vertebral shape.[7] This study, however, did not include local data regarding the bone mineral density following treatment.

The best way to measure bone mineral density is through the use of dual energy x-ray absorptiometry (DEXA). Due to the prohibitive costs, patients are unable to undergo this procedure. A readily available and cheaper alternative is measurement of the metacarpal index. A good correlation has been found between metacarpal index and DEXA.[19]

This study seeks to determine the change in bone mineral density measured through metacarpal index after 6 months of intravenous bisphosphonate (pamidronate) treatment in patients with OI. Secondary parameters are to report the number of fractures sustained per month while on pamidronate therapy and to describe any adverse reactions to pamidronate therapy.

Methods

This is a retrospective study of six pediatric patients between the ages of 1 year and 10 months-9 years and 9 months old diagnosed with moderate to severe OI seen at the UP-PGH from January 2006 to June 2011 who have undergone six months of pamidronate therapy or a total of 6mg/kg and have available pre- and post-treatment radiographs. The diagnosis of osteogenesis imperfecta was made based on clinical and radiographic features. The study was reviewed and approved by the Ethical Review Board of the UP-PGH.

Indications for initiating pamidronate therapy include patients with Type III or severe OI and other types of osteogenesis imperfecta where there are recurrent long bone fractures, vertebral crush fractures, long bone deformity, bone pain or low bone mass.[20] Patients are given a priming dose of 0.5mg/kg before the intestive phase of therapy. During the intensive phase, pamidronate is given at a dose of 1mg/kg monthly for the first six months then every two months at 1.5mg/kg/dose for three cycles. If clinical improvement is noted after a year, the therapy may be given every two months at 1.5mg/kg/dose for one year. After the second year of infusion, the maintenance phase is started. The dosage and duration of intervals depend on the patient's age.

Retrieval of the charts of the patients was done and baseline characteristics (age, sex, type of osteogenesis imperfecta, weight, height/length, Vitamin D levels, serum calcium, magnesium, phosphorus, alkaline phosphatase, creatinine, and BUN levels) were noted. Adverse events during treatment and fracture incidence (reported as fractures per month) were noted. Fracture incidence is defined as the number of fractures sustained in the six months prior to treatment initiation and throughout the treatment period.

The estimation of bone mineral density was done through the measurement of metacarpal index.[21] Patients' left hand x-rays taken from their first consult served as baseline or pre-treatment x-rays and their x-ray after the sixth month of treatment were retrieved. These radiographs are taken as a monitoring tool to assess response to treatment per pamidronate therapy protocol of the UP-PGH Section of Genetics. A total of sixteen radiograph films from seven patients were retrieved. The metacarpal indices were measured by a radiologist who was blinded to the identities of the patients.

The metacarpal index was computed as the ratio of the cortical thickness of the radial side plus the cortical thickness of the ulnar side and the outer diameter of the bone, specifically the 2nd metacarpal of the left hand. It was also defined by the equation: outer cortical diameter – inner cortical diameter divided by the outer cortical diameter[22] (Figure 1). The inner and outer diameters were measured at the midshaft location using a vernier calliper with a gradation of 0.05mm in the vernier scale. Three measurement trials for each of the plates were done and recorded.

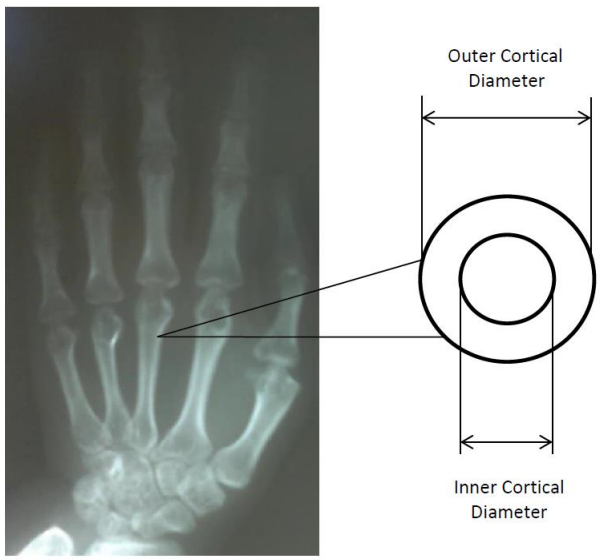

Figure 1. Measurement of the metacarpal index.

The pre- and post-treatment metacarpal indices were analyzed using a paired t-test and estimated at 95% confidence interval. The mean difference, standard deviation, and standard error were calculated using the STATA 9.0.

Results

Of the seven patients who passed the inclusion criteria, only six were included in the analysis. The pre-treatment radiographs of one patient were unfit for analysis because they did not exhibit the posteroanterior projection of the left hand which is needed to measure the metacarpal index.

The six patients included in the study consisted of two female and four male patients. Two patients are classified to have OI type IV (moderate) and four are classified to have OI type III. The patient's baseline characteristics are listed in Tables 1 and 2.

There is note of an increase in the metacarpal index in five of the six patients. However, when results are subjected to statistical analysis using a paired t-test with a confidence interval of 95%, the increase in the metacarpal index is not significant (Table 3).

All patients tolerated the infusions and there were no reported adverse reactions to the intravenous bisphosphonate. Only one patient reported a fracture during the six months of treatment (Table 4).

Table 1. Baseline Characteristics of Patients (n=6).

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	1 yr 10 mos	8 yrs	4 yrs	9 yrs 7 mos	8 yrs 6 mos	3 yrs 9 mos
Weight (kg)	5.8	8.5	7.3	12	12	12.5
Length/Height (cm)	63	60	64	97.8	81	92.5
Vitamin D level (mg/ml)	29.4	60	16.6	-	28.3	-
Seurm calcium (mmol/L)	2.61	2.41	2.68	2.28	2.17	2.7
Serum magnesium (mmol/L)	0.85	0.80	1.13	-	0.91	-
Serum phosphorus (mmol/L)	1.34	1.52	1.38	1.77	1.1	1.5
Serum alkaline phosphatase (mmol/L)	489	-	130.96	183	333	286
Serum BUN (mmol/L)	1032	-	5.13	3.82	3.4	3.69
Serum creatinine (umol/L)	1	-	57.91	32	33.8	12.2
Baseline Metacarpal index (mm)	0.22	0.21	0.11	0.49	0.48	0.47
Fractures (6 months prior to treatment)	2	1	2	0	0	1

Table 2. Consolidated Baseline Characteristics of Patients

Variable	Observed	Mean	Standard Deviation	Minimum	Maximum
Age (years)	6	5.958333	3.183617	1.833333	9.75
Weight (kg)	6	9.683333	2.994272	5.8	12.5
Length/Height (cm)	6	76.38333	16.37442	60	97.8
Vitamin D level (mg/ml)	4	33.575	18.54443	16.6	60
Seurm calcium (mmol/L)	6	2.475	0.173292	2.28	2.7
Serum magnesium (mmol/L)	4	0.9225	0.154354	0.8	1.13
Serum phosphorus (mmol/L)	6	1.438333	0.271766	1.1	1.77
Serum alkaline phosphatase (mmol/L)	5	284.392	139.6885	130.96	489
Serum BUN (mmol/L)	5	3.472	1.374216	1.32	5.13
Serum creatinine (umol/L)	5	27.382	20.58943	1	57.91
Baseline Metacarpal index (mm)	6	0.33	0.168879	0.11	0.49
Fractures per month (6 months prior to treatment)	6	0.17	0.1520526	0	0.34

Table 3. Comparison of baseline levels and levels six months after pamidronate therapy.

	Metacarpal index before therapy	Metacarpal index after 6 months of therapy	Paired t-test
N	6	6	6
Mean	0.3300	0.3833	0.053 (-0.11, 0.117) p-value = 0.0874
Standard deviation	0.1689	0.1512	0.0612
Standard error of measurement	0.0689	0.0617	0.025

Table 4. Comparison of fracture incidence six months prior to initiating pamidronate therapy and while undergoing pamidronate therapy.

Variable	Observed	Mean	Standard Deviation	Minimum	Maximum
Fractures per month (6 months prior to treatment)	6	0.17	0.1520526	0	0.34
Fractures per month (during treatment)	6	0.057	0.1388044	0	0.34

Discussion

Medications used in OI increase bone strength either by increasing the amount of bone protein matrix or by increasing bone mineralization via reduction in bone remodelling.[8] The use of bisphosphonates, either orally or intravenously, represents a major advance in the treatment of osteoporotic disorders.[23] Cyclic intravenous pamidronate is currently the most widely used medical therapy for children with moderate to severe OI.[2]

This retrospective analysis of six patients with moderate and severe OI who underwent intravenous pamidronate therapy for six months demonstrated an increase in bone mineral density as evidenced by an increase in the metacarpal index. Although the increase is not statistically significant when subjected to analysis, the increasing trend shows favourable results. The follow-up period of six months may have been quite early to show any statistically significant change. A study by Kusumi et al[24] have shown statistically significant results in the bone mineral density measured through lumbar spine DEXA among children under 24 months of age with OI receiving pamidronate therapy after one year of treatment.

Similar studies on the use of pamidronate in children have shown an increase in bone mineral density compared to baseline.[8,14-16,23-27] It must be noted however, that these studies made use of DEXA to measure bone mineral density in the lumbar spine. Due to the expense of this procedure, the patients in this study did not have this done.

A study by Glorieux et al,[14] reported an increase in the metacarpal width 27$\pm$20.2% increase per year from baseline following pamdironate infusion every 4-6 month intervals for 1.3-5 years. This study show slightly better results with an increase in the metacarpal index post-treatment by 16% (in 6 months) compared to the reported 13% increase (in 6 months). The increased values show an improvement in the patients' osteopenia.

It is noted that in Glorieux et al's study, the pamidronate infusion was given for three consecutive days and overall, the children in their study received a mean of 6.8$\pm$1.1 mg/kg/year with an initial interval of 6 months between cycles. The six subjects included in the study received a higher dose of pamidronate at 6mg/kg over a period of 6 months. They also underwent infusions at shorter intervals (monthly). These differences may account for the slightly better results.

The cyclic administration of intravenous pamidronate reduced the incidence of fracture.[1,14,16] In this study, four out of the six subjects reported fractures six months prior to therapy. While treatment was on-going, only one patient reported a fracture. Salehpour[1] cautions that fracture incidence is a weak efficacy parameter because it can be influenced by external factors including mode of handling, and mobility, and may spontaneously decrease with age. Since the subjects in this retrospective review were not compared to the fracture rate in an age-matched control group, it is difficult to ascertain whether the decrease in fracture can be attributed to pamidronate alone.

Despite encouraging results, safety issues are a concern when bisphosphonates are administered to children and adolescents.[22] Reported side effects include transient flu-like symptoms occurring 12-36 hours post infusion, drop in serum calcium concentrations and other adverse drug reactions.[8,22] In this study, there are no reported adverse reactions following pamidronate therapy, possibly due to the administration of Ibuprofen prior to starting the pamidronate infusion, as stated in the UP-PGH protocol.[20] Despite the absence of side effects, however, it is important to continue monitoring these patients during subsequent cycles.

Limitations and Recommendations

The study only included patients whose pre- and post-treatment radiographic plates were available. This study could have included additional patients but their radiographs were no longer available as x-ray plates older than 5 years old were discarded.

This study shows that although there is an increase in the metacarpal index of the patients, the increase is not statistically significant. It is recommended that the patients be followed up for a longer period of time. Another recommendation is to increase the sample size. Using the computed standard deviation of 0.0612, a statistically significant change (delta = 0.04) with a 95% confidence interval may be reached with a population of 12 patients.

The available radiographs were taken using different x-ray machines. While bone mineral density calculation was not noticeably affected by changes of film-focus distance, exposure level or film sensitivity/film brand it was influenced by the tube voltage.[28] Further, it is difficult to define the exact location of the endosteal surface of each metacarpal shaft. Digital x-ray imaging is suggested because this defines the bone edges more accurately, anatomic landmarks are identified automatically, and multiple measurements can be done quickly.[13]

Conclusion

Overall, the results of this study concurs with the results of previous studies which showed that among patients with osteogenesis imperfecta who received intravenous pamidronate therapy, an increase in bone mineral density and a decrease in fracture rate is expected and that intravenous bisphosphonate therapy is generally well tolerated.

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