Research Article

Clinical Profile and IV Bisphosphonate Therapy in Children with Osteogenesis Imperfecta in Cipto Mangunkusumo Hospital.

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Abstract:

Introduction: Osteogenesis imperfecta (OI) is a rare genetic disease affecting type I collagen in bone and skin. There is currently no cure for OI; however, studies showed that bisphosphonate administration confers some benefits. We aimed to know the characteristics of OI patients and the correlation between bisphosphonate therapy and fracture incidence.

Methods: We conducted a retrospective cross-sectional study from the OI registry database in Cipto Mangunkusumo Hospital. Acquired data from the registry and medical records were analyzed.

Results: As many as 41 OI patients received intravenous (IV) bisphosphonate therapy. Twenty-five subjects had sufficient data for analysis. The fracture frequency and rate pre and post therapy decreased from 4 (1-20) to 1 (0-10) and from 1.2 (0.17-9) to 0.57(0-2), consecutively. Positive significant correlation were found between duration of therapy and fracture frequency post therapy (p= 0.04), duration of therapy and fracture frequency difference (p=0.028), frequency of therapy and fracture frequency post therapy (p=0.03), and frequency of therapy and fracture frequency difference between pre and post therapy. (p=0.046).

Conclusion: The fracture frequency difference pre and post therapy increased along with the frequency and duration of IV bisphosphonate administration. This conclusion supports the benefit of IV bisphosphonate therapy in OI children. However, the reduction of fracture incidence in pediatric OI receiving intravenous bisphosphonate therapy is still inconclusive.

Keywords: osteogenesis imperfecta, intravenous bisphosphonate, fractures, children

INTRODUCTION

Osteogenesis imperfecta (OI) is a rare genetic disease caused by mutations in genes which encode type 1 collagen; the major component of bone and skin extracellular matrix. As a result, it causes bone fragility and susceptibility to fracture with minimal or no trauma. OI is the most common cause of primary pediatric osteoporosis. In the United States, there were approximately 500,000 patients with OI. It is estimated that one in every 100,000 children worldwide is born with OI. In Indonesia, the prevalence of OI is still undetermined. For the past five years, the Endocrinology Division, Child Health Departement, Cipto Mangunkusumo Hospital (CMH) recorded 70 patients with OI.

OI is classified into several types; the most common etiology is mutation of COL1A1 or COL1A2 gene. Approximately 10-15% of cases with similar clinical manifestation do not show mutation of these genes, but rather genes that interact with type I collagen, for example BMP1, TMEM38B, and WNT1.1, The triad clinical manifestation of OI is fragile bone, blue sclera, and premature hearing problem. OI also frequently manifests as joint hypermobility and dentinogenesis imperfecta.

In 1979, David Sillence classified OI into four types based on clinical manifestations and radiologic features. Afterwards, two more classifications with different histologic features were added, type V and type VI. Meanwhile, type VII to type XII of OI was classified based on molecular abnormalities followed by its clinical characteristics. 2,5Although the pathogenesis and pathophysiology of OI is well-known, this disease is incurable and current management are supportive to increase quality of life.3 One available treatment routinely administered for OI is bisphosphonate which prevents bone resorption. There are two types of Bisphosphonate, nitrogenous and non-nitrogeneous. Nitrogenous bisphosphonate interrupts osteoclast formation, survival, and cytoskeletal dynamics. Non-nitrogenous bisphosphonate promotes osteoclast apoptosis. Each bisphosphonates have different efficacy and absorption.3 Many studies showed improvement of BMD and decrement of pain in OI children treated with bisphosphonate. However, there are not enough data to support the role of bisphosphonate in reducing the incidence of clinical fractures.3 Our study aimed to investigate the clinical characteristics and the correlation between bisphosphonate administration and fractures frequency difference pre and post therapy in children with OI in CMH.

METHODS

We conducted a retrospective cross-sectional study on OI children less than 18 years old who received bisphosphonate therapy infusion in Cipto Mangunkusumo Hospital (CMH), Jakarta, Indonesia. We reviewed data from the OI registry and medical records from April to October 2018. OI was diagnosed based on clinical manifestation and radiologic features. At the time of study, molecular genetic analysis was not commonly carried out on OI patients in CMH due to lack of funding.

Subjects included in this study had received bisphosphonate infusion (Pamidronic or Zoledronic Acid) at least once. Data assessed from medical records included the type of OI, age at diagnosis, family history, health funding, clinical features (multiple fractures, blue sclera, long bone deformity, vertebrae deformity, and short stature), age at first therapy, duration of therapy, frequency of bisphosphonate administration, and clinical fractures frequency and fracture rates pre and post therapy.

We determined the outcome of fracture rate pre therapy by dividing clinical fracture frequency pre therapy and age at first therapy, whereas fracture rate post therapy was obtained by dividing clinical fractures frequency post therapy and duration of therapy. Then, we calculated difference between fracture frequency pre and post therapy as an improvement parameter. Descriptive analyses were conducted to determine the mean or median. Prior to statistical analysis, data distribution was tested using Shapiro-Wilk Test. If the distribution was normal, data were tested using Pearson correlation. Otherwise, Spearman correlation was used. We also conducted analyses to determine whether there were differences in clinical fractures between OI types (type I, type III, and type IV) Data were analyzed using SPSS (Version 20 for Mac). No ethical approval for the protocol was indicated, as this study was a retrospective non-interventional medical record review and anonymity of subjects were ensured. All data collected and analysed were routine diagnosis and treatment based on national guidelines, no new protocols were implemented. Study approval from the research and development of Child Health Department, Faculty of Medicine University of Indonesia – Cipto Mangunkusumo Hospital was obtained.

RESULTS

Characteristics of subjects

A total of 41 OI patients who received IV bisphosphonate were acquired from the hospital registry and medical records. However, only 25 patients had sufficient data of clinical fractures frequency pre and post therapy. Clinical characteristics of subjects are presented in Table 1. Subjects were 0-18 years old with median age of 6 years. Patients' age at diagnosis median were less than 1 year old with the oldest age at diagnosis of 10 years old. The male-to-female ratio was of 1:1.16. Patients were mostly funded by the Indonesian national insurance (39/41). All patients were admitted for hospitalization because bisphosphonate treatment was only covered by the national health insurance for inpatients.

The majority of patients had moderate-severe or type 3 OI (61%). A quarter of the subjects had family history of OI (11/41). All patients had history of multiple fractures (41/41) and 30 patients (73.2%) presented with blue sclera. The majority of the patient presented with long bone deformation (40/41) and 18 patients (43.9) with spine deformation. Almost all patients had short stature (92.7%). Bone mineral density (BMD) was examine in less than half of subjects (14/29). All patients were discharged after bisphosphonate administration because no serious and significant adverse effects occurred.

In this study, patients received first bisphosphonate therapy at median age of 2 years and the median duration of therapy was 2 years. The median frequency of bisphosphonate administration was 5 times and the median frequency rate was twice per year. Clinical fractures pre and post therapy reduced from 4 times to 1 time. Clinical fracture frequency rate pre and post therapy also reduced, from 1.2 times per year to 0.57 times per year. The median difference between fracture rate pre and post therapy was 1. We identified a significant correlation between age at diagnose and fracture frequency pre therapy (coefficient correlation: 0.501, p=0.005).

Table 1. Clinical characteristics of subjects

Variables	Values	N
Sex		41
Male	20 (48.8%)	
Female	21 (51.2%)	
Age		
Present (years)	6 (0-18)	41
At diagnosis (years)	0 (0-10)	40
At first therapy (years)	2 (0-12)	41
OI classification by Sillence		41
I	6 (14.6%)	
II	0 (0%)	
III	25 (61%)	
IV	2 (4.9%)	
Unknown	8 (19.5%)	
Health fund		41
National health insurance	39 (95.1%)	
Private	2 (4.9%)	
Family history		41
Yes	11 (26.8%)	
No	28 (68.3%)	
Unknown	2 (4.9%)	
Clinical manifestation		
Multiple fractures	41 (100%)	41
Blue sclera	30 (73.2%)	41
Long bone deformation	40 (97.6%)	41
Spine deformation	18 (43.9%)	30
Short stature	38 (92.7%)	40
BMD		29
Yes	14 (48.3%)	
No	15 (51.7%)	

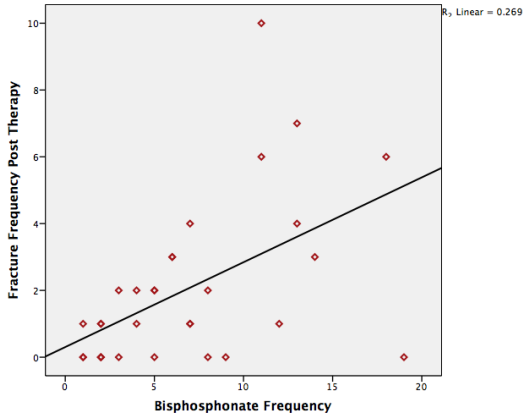
Intravenous bisphosphonate therapy and clinical fracture

Thirty-one patients had data for clinical fractures pre and post therapy. But, only 25 patients had sufficient medical history for clinical fractures pre and post therapy. Exploratory subgroup analysis showed no significant differences in clinical fractures across all OI types. We found significant positive correlation between duration of therapy and fracture frequency post therapy (correlation coefficient = 0.506, p=0.04).

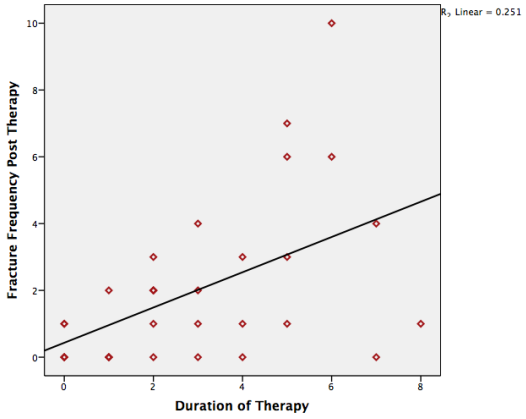
Moreover, we observed a significant positive correlation between bisphosphonate frequency and fracture frequency post therapy (coefficient correlation = 0.519, p=0.03). In this study, there was a significant correlation between duration of therapy and difference of fracture frequency pre and post therapy (correlation coefficient = 0.439, p=0.028). Twenty-one out of 31 patients experienced new fractures after therapy. A positive significant correlation was also identified between bisphosphonate frequency and difference of fracture frequency pre and post therapy (coefficient correlation = 0.403, p =0.046).

Table 2. Bisphosphonate therapy and clinical fracture frequency

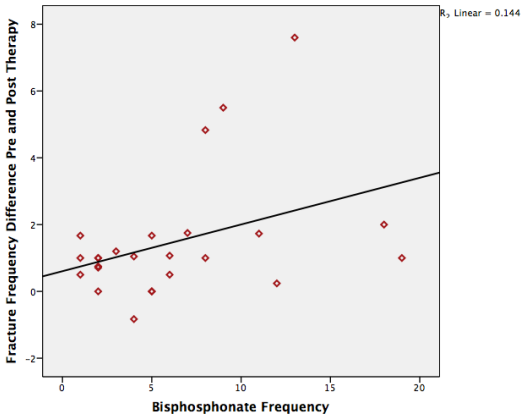
Variables	N	Values	Type I	Type III	Type IV	p
Bisphosphonate therapy						
Duration (years)	41	2 (0-10)	2.67 (±	2.74 (±	6.00 (± 2.83)	0.262
Frequency (times)	41	5 (1-19)	2.07)	2.25)	7.00	0.794
Frequency (times) per year	41	2 (0.5-3.5)	5.5 (± 4.32)	5 (1-19)	1.31(0.62)	0.375
			1.96	2.10(±0.80)		
			(±0.55)			
Clinical fracture						
Before therapy (times)	31	4 (1-20)	7.40(±6.54)	3.50 (1-20)	4.00	0.936
After therapy (times)	31	1 (0-10)	0 (0 -10)	1.5 (0-7)	1	0.384
Rate before therapy (times)	31	1.2 (0.17-9)	2.27(±2.13)	1.29(0.44-9)	2	0.610
Rate after therapy (times)	31	0.57 (0-2)	0.67(±0.61)	0.59 (0-2)	0.19 (0.13-	0.314
Difference of fracture	25	1 (-0.83 – 7.6)	1.96(±0.55)	2.10(±0.80)	0.25)	0.483
frequency (times)					1.31 (±0.62)	



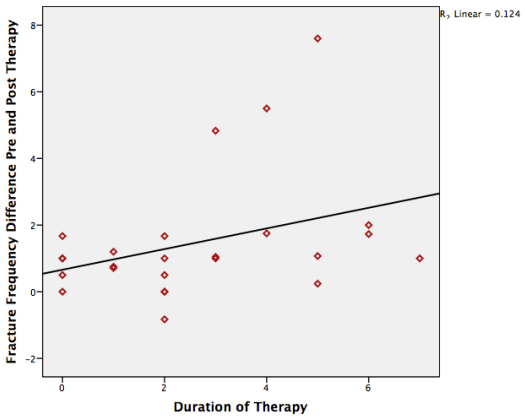
Graph 1 Bisphosphonate frequency and fracture frequency post therapy



Graph 2 Duration of therapy and fracture frequency post therapy



Graph 3 Bisphosphonate frequency and fracture frequency difference pre and post therapy



Graph 4 Duration of therapy and fracture frequency difference pre and post therapy

DISCUSSION

Nowadays, 16 types of OI and similar syndromes are recognized.2,5, The most common type is type I which comprises 60% of OI patients. Patients with type I OI have the mildest clinical manifestation and many are undetected. Type II OI is the lethal type, oftenly the baby is stillborn or dies in the first year. OI type III is considered the most severe non-lethal type and progressively deforming. The manifestations of OI type III are macrocephaly, triangular face, multiple fractures during early childhood, permanent deformities, and delayed motoric development. OI type IV usually has features of grey sclera and shorter stature than type I.2,5

Type I collagen is the major protein composing bone and also can be found in ligaments, tendons, dentin, sclera, and skin.3 Typical bone matrix is made up of 90% type I collagen fibers and 10% non-collagenous proteins.3 Collagen fibers are usually found in alignment with hydroxyapatite; crystals located within the fibers.3 Hydroxyapatite crystals have function to give strength and rigidity to bone, meanwhile collagen fibers flexibility.3

OI diagnosis and treatment remains a challenge in Indonesia, as the awareness in healthcare workers and population is still low and not all examinations are funded by the national health insurance. The real incidence of OI is not yet known, there are no current national data and many patients are predicted to be undiagnosed.

Clinical Characteristics In this study, we found 41 patients who received bisphosphonate therapy in CMH although only 25 were included for further analysis. The current median age of patients was 6 (0-18) years, while at diagnosis the median was 0 (0-10) years. The latter is lower than a study in Egypt by Hamza, et al which reported the age at presentation to be 5.25 (0.7-11.8) years. There was no significant difference in male-to-female ratio, similar to previous studies in Egypt and Vietnam.7, In Taiwan, a female preponderance was found with the ratio of 2.2:1.

The majority of patients in this study were classified as type 3 (61%). In contrast, Binh, et al8 in Vietnam found nearly equal percentages of OI type 1, 3, and 4 (31.51%, 31.51%, and 36.98%) in their study

population. Lin et al also found that most patients were classified as either type I (39.56%) or type IV (39.56%). Family history of OI was high, reaching almost a quarter of the subjects. Brizola et al in Brazil reported an even higher number, family history in all types of OI reached 44.6%, highest in type 1 (66.7%). A previous study in China also found positive family history in 54% subjects.

Blue sclera presented in 73.2%, in accordance with previous studies.8,11 Bone deformities in OI patients mostly affect in the lower limbs because of excess bone malleability and plasticity. Deformities in the upper limbs and skull are less common. In this study, long bone deformity was observed in almost all patients (97.6%). Short stature was found in 92.7% patients in this study, higher than previous study in Egypt (39.28%).7 Aglan et al found that approximately 90% of type III patients had short stature, while in type I and IV the percentage was lower, 30% and 75%, respectively. A parallel relation was also determined between OI severity and the degree of short stature.

Although decreased BMD is not specific for OI, BMD should be examined in all OI patients for diagnostic, prognostic, and therapeutic purposes. In this study, BMD was examined in approximately half of the patients (48.3%). This low number is estimated to be affected by the high cost and BMD is not yet funded by the national health insurance.

Bisphosphonate therapy and clinical fracture

Bisphosphonate therapy both oral and intravenous has been the most promising pharmacologic therapy for children with OI. Along with orthopedic management, physiotherapy, rehabilitation, and other pharmacologic agents including growth hormone, calcitonin, parathyroid hormone, sodium fluoride, and vitamins were administered in attempts to reduce fractures and improve quality of life.3 Bisphosphonate mechanism of actions were to alter balance in bone remodeling so that the bone resorption reduced.

OI therapy administered in this study was the most widely used IV bisphosphonate, pamidronic acid (PA) or zolendronic acid (ZA). Pamidronic acid was available in CMH before 2014. Since 2014, zolendronic acid has been the choice of bisphosphonate therapy and is covered by the national insurance. Compared to pamidronic acid, zolendronic acid is 850 times more potent with a longer dosing interval. In this study, seven children had received PA before they started to receive ZA in 2014.

Pamidronic acid was given with the annual dose of 9 mg/kg every 2 months for OI children 2-3 years old and every 4 months for children older than 3 years old. Meanwhile, ZA was administered with dose of 0.025 to 0.05 mg/kg within 6 to 12 months interval. The annual dose of ZA was 0.1 mg/kg. Bisphosphonate treatment could be interrupted for at least 4 months after orthopedic surgery such as osteotomies to provide bone healing. However, the treatment schedule was not delayed after fractures.

Many studies observed the administration of bisphosphonate therapy in OI children; one of the primary outcomes was fracture rate.3 Clinical outcome of fractures is the ideal results to observe bisphosphonate

therapy. However, it requires great effort since OI is a rare event, many studies substitute BMD as the outcome. Various studies of bisphosphonate therapy had been conducted, however there were no apparent conclusion whether it significantly reduced the fracture rate or not.3

We identified a positive significant correlation between duration of therapy and fracture frequency post therapy (p=0.04). Additionally, there was a positive significant correlation between bisphosphonate frequency and fracture frequency post therapy (p=0.03). In other words, the longer duration of bisphosphonate therapy, more clinical fractures occurred. This might be caused by new fractures during the treatment, increased activity, and progressive deforming on severe types of OI. However, this study neither included the cause of fractures events nor assessed quality of life of subjects. No significant difference of fracture rates and frequency across OI type were identified in this study, therefore all OI patients with bisphosphonate therapy were included in the analyses. Despite the fact that reduction in fracture frequency pre and post therapy was not significant, we observed that the medians of clinical fractures frequency and fractures rate pre and post therapy reduced from four times to once and from 1.2 to 0.57, respectively.

Feehan et al conducted a cohort study comparing adults with OI who were treated with bisphosphonate and never treated during childhood (control group). There was significant result of fracture incidence reduction in pre pubertal OI patients in treated group. The post pubertal fracture incidence was higher in less severe due to increase levels of physical activity and functioning. 14 Falk et al15, reported that new fractures occurred in all patients receiving therapy and this may be due to mobility improvement and increased activity. It was also identified that moderate to severe trauma caused the fractures. Many studies on bisphosphonate therapy in OI children reported reduction of fracture rate between pre and post therapy. In contrary, a systematic review by Dwan, et al3 signified that although oral or IV bisphosphonates significantly increased spine BMD statistically, change in fractures incidence after therapy was still unclear. The studies stated that retrospective fracture recall could lead to potential recall bias. Furthermore, studies that evaluated fracture frequency or rate as an outcome requires an enormous number of subjects, but this is not possible since OI is a rare disease with a small population.

This study also observed that difference of fracture frequency pre and post positively increased along with the duration and frequency of therapy. We found no similar study which searched for the correlation of duration or frequency of bisphosphonate with change in fracture rate after therapy. Vuorimies, et al studied femoral fractures in the pediatric population with OI and found that bisphosphonate administration did not alter the pattern of femoral fractures. Instead, the different characteristics of femoral fracture were associated with clinical subtype of OI.

Another study by Letocha, et al showed that after two years of therapy, the fracture rate did not reduce in the upper (p= 0.840) or the lower extremities (p=0.290). A two-year observational study of ZA administration in OI and Bruck Syndrome by Otaify, et ale showed significant reduction of fractures frequency after 6 and 12

months of follow up. The reduction of fracture incidence as the primary outcome of bisphosphonate therapy is still not fully perceived.

Currently, there is no established consensus regarding the optimal duration of bisphosphonate therapy in OI children.16 In this study, the longest treatment duration was 10 years, longer compared to other studies.3 A study in adults reported that prolonged bisphosphonate therapy reduces osteoclastic bone remodeling and was associated with atypical femur fractures, but no similar case has been reported in children with bisphosphonate treatment.16

No significant or serious adverse events were recorded in this study. No studies have investigated the long-term efficacy and safety for bisphosphonate therapy in pediatric group.16 Rijks et al suggests that short-term (3 years or less) bisphosphonate administration was well tolerated. , A study observed the short term safety of ZA and found that adverse effects such as fever, flu-like symptoms, myalgia, and bone pain were common. These adverse effects were more frequent in pediatric subjects receiving initial ZA infusion compared to subsequent infusions. To date, bisphosphonate-related osteonecrosis of the jaw (BRONJ) has not been reported in the pediatric population. The pathogenesis of BRONJ is currently being studied; risk factors include duration of bisphosphonate treatment, intravenous bisphosphonate, dental procedures or trauma, and underlying cancer.

Oral bisphosphonate is not commonly used in Indonesia at the time of study. Lv, et al compared the use of oral versus intravenous bisphosphonate in children with OI, and found that IV zoledronic acid once a year and oral alendronate similarly increased BMD and reduced bone resorption. Intravenous bisphosphonate administration had better outcome in clinical fracture rate.

A few limitations of this study include a small number of subjects and data were secondary from medical records. There was bias in recalling clinical fracture events and no radiological confirmations data were recorded. Furthermore, this study should have differentiated between clinical subgroups since the progression is different. We recommend the conduction of randomized controlled trials (RCT) with fracture as the endpoints with adequate number of subjects.

CONCLUSION

Reduction of fractures incidence as the primary outcome of bisphosphonate therapy in OI children is still inconclusive. Our results support the benefits of bisphosphonate therapy, shown by the significant correlation between duration of therapy and change of fracture frequency pre and post therapy. Additionally, our study also found that the frequency of bisphosphonate therapy correlated significantly with greater change of fracture frequency pre and post therapy. Although duration and frequency of therapy had positive correlation with fracture frequency post therapy, these might be caused by improvement of activity, mobility, and quality of life, which were not assessed in this study. Furthermore, bisphosphonate administration was

found to be safe. Future studies should be conducted to determine the risk factors of fracture occurrences after bisphosphonate therapy, such as increased activity and the severity of OI. Follow-up studies are needed to determine the effects, optimal dosing, and long-term efficacy and safety of intravenous bisphosphonate therapy in pediatric OI.

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