Clinical Outcome of Patients with Osteogenesis Imperfecta on Intravenous Pamidronate Treatment at the Philippine General Hospital from 2010-2018

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ABSTRACT

Background. Osteogenesis imperfecta (OI) is a group of connective tissue disease characterized by propensity to fractures following minimal trauma. OI is a lifelong inheritable disease and currently has no definitive cure. Management goals are directed towards prevention of fractures, controlling the symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength. Bisphosphonates are the mainstay of pharmacologic fracture-prevention therapy for most forms of OI. The University of the Philippines-Philippine General Hospital Bisphosphonate Treatment Program for OI was started in 2006 by the Clinical Genetics Service. For more than a decade now, the program has been serving more than 50 OI patients. This study evaluated the clinical outcomes of the patients who were included in the program to add to the body of knowledge on Filipino patients with OI.

Objectives: This study sought to determine the clinical outcomes of children with OI on intravenous pamidronate treatment at the Philippine General Hospital (PGH) from January 2010 to December 2018.

Methods. The study utilized a retrospective review of medical records of 24 patients diagnosed with OI on pamidronate therapy seen at the PGH from January 2010 to December 2018. Descriptive statistics were used to summarize the demographic and baseline clinical characteristics of the patients. Median annualized fracture rates before and during treatment were calculated and compared. The patient functional mobility before and during pamidronate infusion was classified accordingly based on the Gross Motor Function Classification System (GMFCS) and were compared.

Results. Twenty-four patients, which include seven males and 17 females, with ages at the time of conduct of the study ranging from four years to 11 years, fulfilled the inclusion criteria. There were four patients with OI type I, six with OI type III, 11 with OI type IV and three with OI type V. The annualized long bone fracture rate decreased significantly from a median of 2.0/year (range 1-2.75) to 0.75/year (range 0-1) after more than a year on pamidronate infusion ($p<0.001$). There is a note of overall improvement in terms of functional mobility using the 5-point scale of the GMFCS during pamidronate infusion from the baseline. However, the difference is not statistically significant.

Conclusion. Cyclic intravenous pamidronate treatment in young children with moderate-severe OI is well tolerated and associated with reduced fracture frequency with a tendency to improvement of gross functional mobility.

Keywords: osteogenesis imperfecta, pamidronate infusion, bisphosphonate

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INTRODUCTION

Osteogenesis imperfecta (OI) is a group of heterogeneous genetic connective tissue disorder characterized by bone fragility and low bone mass with increased susceptibility to bone fractures.[1-3] Other clinical features include bone deformity, blue sclerae, short stature, joint hypermobility, hearing loss, and dentinogenesis imperfecta.[4] In 1788, Olaus Jakob Ekman gave OI its first scientific description in his dissertation on *congenital osteomalacia*.[5] Important studies and researches on OI ensued through the years that include classification of OI into the four Sillence types and establishment of defective collagen type 1 biosynthesis as the major cause of OI, with subsequent detection of recessive genetic variants causing minority of the cases.

The first OI classification by Professor David Sillence described four types according to clinical, radiological, and genetic features.[6] Type I was described as mild, dominantly inherited OI with blue sclerae; Type II as lethal, perinatal, recessively inherited OI with characteristic radiographic features; Type III as progressively deforming, recessively inherited OI with normal sclerae; and Type IV as dominantly inherited OI with normal sclerae. It has since then expanded to include novel types V, VI and VII, which were derived from the complex and heterogeneous type IV.[4]

Approximately 90 percent of the cases of OI result from mutations in the COL1A1 or COL1A2 genes that encode alpha chains of type I collagen which lead to an increase in osteoclastic activity and a reduction in formation of new bone and greater liability to fracture.[7,8] More recently, other types were added as bone histomorphometry and molecular analysis have been more widely available. By 2018, there were 19 types of OI that have been identified according to clinical features, molecular mutations, and inheritance pattern.[9] Regardless of type, the clinical expression is primarily that of osteopenia, bone fragility, frequent fractures, progressive deformity, loss of mobility, and chronic bone pain.[10]

The first genetic cause of autosomal recessive lethal OI that does not have primary collagen mutation was discovered in patients with CRTAP gene mutation in 2006.[11] Since then, several classifications have been proposed to take into account the genetic complexity and phenotypic variability of OI. In 2011, the Nosology Group of the International Society of Skeletal Dysplasias recommended maintaining the Sillence classification into five OI types based on the degree of severity, regardless of their molecular reference. The several genes and syndromes that can also cause OI were then listed separately.[12]

The reported incidence rate of OI is between 1/10,000 and 1/25,000 worldwide.[1] According to the data available from the Philippine Osteogenesis Imperfecta Support Group, as of August 2017, there are a total of 93 diagnosed patients in the Philippines – 72 in Luzon, 15 in Visayas, and six in Mindanao. The database of the Division of Clinical Genetics, Department of Pediatrics at the University of the Philippines-Philippine General Hospital (UP-PGH) shows that there are around 90 clinically diagnosed patients with OI as of December 2018, 41 of which received pamidronate infusion. Of these 41 patients, seven have OI type 1, 12 have type III, 16 have type IV, and six have type V.

Ideally, the diagnosis of OI is confirmed by identifying pathogenic variants in *COL1A1, COL1A2* and more than 20 other genes associated with OI phenotype.[13] However, diagnosis may be done, especially in resource-limited settings, based on clinical and radiographic features. Confirmatory tests, such as biochemical or molecular tests, can be carried out to confirm the diagnosis in certain situations. In patients with positive family histories, prenatal screening using ultrasound generally have high detection rates.[1]

OI is a lifelong inheritable disease and currently has no definitive cure. Management goals are directed towards prevention of fractures, controlling the symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength.[14]

Bisphosphonates are the mainstay of pharmacologic fracture-prevention therapy for most forms of OI. Bisphosphonates are stable analogs of pyrophosphate and are potent inhibitors of bone resorption and bone turnover by their action on the osteoclasts.[15,16] When bone destruction slows down, osteoblasts, the bone-forming cells, lay down more bone, albeit with the defective collagen, leading to thicker bone which is less prone to fractures. The majority of information about the use of bisphosphonates in OI comes from studies of cyclical infusions of pamidronate in various regimens in children with OI. These reports have noted increased bone mineral density (BMD), decreased fracture rate, and improved functional abilities, mobility, ambulation, and pain, without negative effects on fracture healing or growth rate when used in young children.[17-22]

The UP-PGH Bisphosphonate Treatment Program for OI was started in 2006 by the Clinical Genetics Service. The treatment protocol was adapted from the bisphosphonate treatment protocol used at the Children's Hospital at Westmead (Westmead, New South Wales, Australia).[14] This is currently being offered at the UP-PGH, Vicente Sotto Memorial Medical Center in Cebu, and Southern Philippines Medical Center in Davao, and in a few private hospitals with clinical geneticists. For more than a decade, the program has served more than 50 OI patients. A study by Alcausin et al. in 2011 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.[14] It has also been shown to improve patients' comfort and function.[3,21] Furthermore, the study of Abacan et al., though not statistically significant, demonstrated increased in BMD in six Filipino OI patients after six months of bisphosphonate treatment as evidenced by an increase in the metacarpal index.[10] This present study evaluated the program and increased the body of knowledge on the clinical

characteristics and outcome of Filipino patients with OI undergoing pamidronate infusion.

This study sought to report the outcome of these patients after more than a decade of the program. The outcome measures of interest pertinent to the study include annual fracture rate and functional mobility of OI patients undergoing pamidronate infusion. The functional mobility of the participant as described in the chart was classified accordingly based on the Gross Motor Function Classification System (GMFCS) that was developed by Palisano and colleagues. The GMFCS was initially used for cerebral palsy (CP) patients based on self-initiated movement, with emphasis on sitting, transfers, and mobility. It is a criterion-based, 5-point scale used to evaluate changes in gross motor function in children with developmental disabilities, with Level I, representing the gross functional mobility without limitations, to Level V depicting severe limitations.[23] The GMFCS has also been shown to be a reliable and safe tool for children with OI.[24]

METHODS

This study sought to determine the clinical outcomes of children with OI on intravenous pamidronate treatment at the UP-PGH from January 2010 to December 2018. Specifically, this study aimed to describe the baseline characteristics of OI patients who underwent pamidronate infusion, determine and compare the annualized fracture rate of OI patients before and during intravenous pamidronate treatment, and to establish the functional mobility of OI patients before and during intravenous pamidronate treatment. This study was limited to the data obtained from the charts of patients with OI managed at the UP-PGH.

A retrospective review of medical records of patients with OI seen at the Division of Clinical Genetics, Department of Pediatrics, UP-PGH was utilized. Charts of patients were retrieved from the Medical Records Section of the UP-PGH.

Apart from the three siblings with molecular confirmation of OI Type V, the diagnosis and classification were based on clinical presentation and radiologic features. Patients with OI ages 1-18 years who underwent pamidronate infusion for more than a year were included in the study. Patients who were lost to follow-up for more than one year without pamidronate infusion and OI patients with other chronic diseases (i.e., leukemia) were excluded in the study.

Data obtained included demographics, baseline anthropometric measurements, baseline functional or motor ability, number of fractures during the year prior to the start of treatment, and results of skeletal survey, renal ultrasound, baseline complete blood count, serum calcium, phosphorus, magnesium, alkaline phosphatase, blood urea nitrogen, and creatinine. Adverse events during treatment were also noted. Fracture incidence was calculated using fractures documented on medical records. Fractures were categorized as long bone or vertebral fractures. Only long bone fractures were counted and used in the analysis. In computing the median annualized fracture rate, the number of fractures occurring within the review period was converted and expressed as the number of fractures per year for both before and during treatment. Interventions done per fracture episode were noted. Reported interventions included intramedullary rodding and orthopedic casting only. The data from the medical records pertaining to the participant's functional mobility during and before treatment were classified accordingly based on the GMFCS.

Descriptive statistics were used to summarize the demographic and baseline clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and interquartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables. For the comparison of prior to treatment to during treatment of the OI patients, in terms of median annualized fracture rate and functional mobility, Fisher's exact test and Wilcoxon signed rank test were used. To compare the median annualized fracture rate per year before and after treatment, Mann-Whitney U test was used. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

Ethical Approval

The study was approved by the University of the Philippines Manila Research Ethics Board under registration number 2019-291-01.

RESULTS

Subjects

Twenty-four patients who passed the inclusion criteria were included in the analysis, of which seven were males and 17 were females. There were four patients with OI type I, six with OI type III, 11 with OI type IV and three with OI type V. Interventions to manage acute fractures included casting and intramedullary (IM) rodding surgery. Sixteen underwent IM rodding surgery, of which majority were OI Type IV (66.7%). Three out of the seven who underwent casting only for acute fractures were OI Type I. Characteristics of the subjects at baseline before bisphosphonate treatment are summarized in Tables 1 and 2. Table 3 consolidated the status of the OI patients before and after treatment.

Fracture History

The annualized long bone fracture rate decreased significantly from a median of 2.0/year (range 1–2.75) to 0.75/year (range 0–1) after more than a year on pamidronate infusion ($p<0.001$). Patients who were placed on IM rods significantly decreased their average annualized fracture rate before and after treatment ($p=0.034$).

Table 1. Demographic and Clinical Profile of the Patients (n=24)

	Frequency (%)
Sex	
Male	7 (29.17)
Female	17 (79.83)
Ethnicity	
Filipino	23 (95.83)
Fil-Am	1 (4.17)
Family History of OI/Recurrent fracture	8 (33.33)
OI Sillence Classification	
Type I	4 (16.67)
Type III	6 (25)
Type IV	11 (45.83)
Type V	3 (20.5)
Intervention	
Intramedullary rodding	16 (66.67)
Type I	1
Type III	3
Type IV	10
Type V	2
Orthopedic casting	7 (29.17)
Type I	3
Type III	3
Type IV	1
Type V	0
Developmental history	
At par with age	10 (41.67)
Cognitively at par with age but with gross motor delay	14 (58.33)
	Mean ± SD; Median (IQR)
Age	7.96 ± 3.71
Age at diagnosis (years)	1 (at birth to 2)
Bisphosphonate (Pamidronate) Treatment	
Age started	3.33 ± 2.80
Years of treatment	4.67 ± 1.72
	Frequency (%)
Dose	
1.5 q 2 months	9 (37.50)
1.5 q 3 months	12 (50)
1.5 q 4 months	1 (4.17)
1.5 q 6 months	1 (4.17)
60 mg	1 (4.17)
	Mean ± SD
Complete blood count	
Hemoglobin (mg/dl)	120.59 ± 11.90
WBC (x 10^9/L)	10.37 ± 3.84
Platelet (x 10^9/L)	401.07 ± 118.88
BUN (mg/dl)	6.16 ± 5.13
Creatinine (mg/dl)	20.18 ± 8.30
Calcium (mmol/L)	3.02 ± 2.21
Magnesium (mg/dl)	1.14 ± 0.58
Phosphorus (mg/dl)	2.66 ± 2.46
Alkaline Phosphate (U/liter)	268.12 ± 124.08

Functional Mobility

There is a note of overall improvement in terms of functional mobility using the 5-point scale of the Gross Motor Function Classification System (GMFCS) during pamidronate infusion from the baseline, however, the difference is not statistically significant.

Table 2. Baseline Systemic Physical Examination of the Patients (n=24)

	Mean ± SD; Median (IQR)
Weight	11.09 ± 9.18
Z-score	-3 (-3 to -1)
Height	75.89 ± 24.32
Z-score	-3 (-3 to -2)
Head circumference	45.28 ± 6.10
Z-score	-3 (-3 to 0)
	Frequency (%)
HEENT	
Bluish sclerae	15 (62.50)
Dental caries	2 (8.33)
Triangular facies	9 (37.50)
Dentinogenesis imperfecta	2 (8.33)
Others	7 (29.17)
Chest/Cardiac	
Pectus carinatum	5 (20.83)
Upper Extremities	
Elbow deformity	3 (12.5)
Bowing of extremities	8 (33.33)
Others	1 (4.17)
Lower Extremities	
Bowing of extremities	13 (54.17)
Leg length discrepancy	2 (8.33)
Others	3 (12.5)

Table 3. Prior and during Treatment Status of the OI Patients

	Before treatment	During treatment	*P*-value
	Frequency (%)		
Functional mobility			0.102
Level I	4 (16.67)	6 (25.00)	
Level II	2 (8.33)	9 (37.50)	
Level III	5 (20.83)	5 (20.83)	
Level IV	10 (41.67)	4 (16.67)	
Level V	3 (12.5)	0 (0.00)	
	Median (IQR)		
Overall Median annualized fracture rate (Fx/yr)	2 (1 to 2.75)	0.75 (0 to 1)	<0.001
IM Rodding Median annualized fracture rate (fx/yr)	2 (1 to 2.75)	0.75 (0 to 1)	<0.001
Casting Median annualized fracture rate (fx/yr)	1 (1 to 4)	1 (0 to 1.5)	0.021
P-value of IM Rodding versus Casting	0.805	0.507	

DISCUSSION

The use of cyclical intravenous bisphosphonates has radically transformed the management of OI over the years. Bisphosphonate use in OI increases bone strength either by increasing the amount of bone protein matrix or by increasing bone mineralization via reduction in bone remodeling.[25] This study does not only support the use of intravenous pamidronate in children with moderate-to-severe OI, but also gives credence to the program instituted by the Division of Clinical Genetics. Replicating results of previous studies[18-23], this study demonstrated a significant decrease in fracture rates and an improvement in the gross functional mobility of OI patients.

Cyclic intravenous pamidronate has been given in various doses with different frequencies.[17-22,26–29] In our institution, indications for initiating pamidronate therapy include patients with moderate to severe OI and other types of osteogenesis imperfecta where there are recurrent long bone fractures, vertebral fractures, long bone deformity, bone pain or low bone mass.[26] Patients are admitted in the wards and given a priming dose of 0.5 mg/kg before the intensive phase. For OI patients less than one year old, admission to the Intensive Care Unit is done for closer monitoring. During the intensive phase, pamidronate is given at a dose of 1 mg/kg monthly for the first six months then every two months at 1.5 mg/kg/dose for three cycles. If clinical improvement is noted after a year, the therapy may be given every two months at 1.5 mg/kg/dose for one year with a cumulative dose of 9 mg/kg/year. After the second year of infusion, the maintenance phase is started with a cumulative dose of 6 mg/kg/year. The dosage and duration of intervals depend on the patient's age and response to treatment. In this study, no one had adverse events apart from fever and flu-like symptoms during the first infusion, which is part of the well-recognized acute-phase reaction seen with bisphosphonate treatment. Respiratory difficulties or symptomatic hypocalcemia were not seen.

Intravenous bisphosphonates have not only been shown to decrease fracture rates, and in combination with physical therapy and timely orthopedic surgery, it also improves the functional outcomes of children with moderate-to severe OI.[17,26] Although there were five OI patients whose gross functional mobility remained static: three stayed in the highest level of mobility function enabling to ambulate without limitations, one with limitations in walking long distances and balancing, and one functions in sitting but self-mobility is limited requiring manual wheelchair during transportation; the overall gross functional mobility of OI patients on pamidronate therapy improved over time. No statistically significant improvement in gross functional mobility in this study may be due to various potential confounders including age at start of bisphosphonate treatment, location of previous fractures and bone deformities prior to treatment, as well as compliance to medical, orthopedic, and rehabilitative interventions.

OI patients in our setting are being treated in a multi-disciplinary approach to maximize their clinical outcomes and function, fulfill their potential, gain independence and well-being.[30] The Division of Clinical Genetics holds a bi-annual multi-disciplinary clinic composed of services from Orthopedics, Rehabilitation Medicine, Allied Medicine, Dentistry, and Adult Endocrinology. The involvement of these subspecialties is vital to the comprehensive team management of these patients.

In this study, more than half of the patients underwent surgical interventions. Surgical interventions include osteotomies and placement of intramedullary rods to correct deformity and to provide internal support to brittle bones. Patients who were placed on IM rods significantly decreased their average annualized fracture rate after treatment. One of the benefits of these surgeries is that some patients who were previously wheelchair-bound due to bony deformity may be able to ambulate.[31] There were two patients in the study whose functional mobility declined after multiple surgeries. One was due to difficulty ambulating due to weight gain. Another one may be due to failure to undergo physical therapy after surgery. This emphasized the importance of co-managing OI patients with Rehabilitation Medicine and Allied Medicine which provide non-surgical interventions such as physical therapy and use of orthotics. Physical therapy may consist of exercises and positioning that aim to prevent contracture, strengthen muscle, and decrease fractures.[30]

Several studies on administration of pamidronate to ages less than 3 years showed that this led to earlier acquisition of motor milestones in comparison to untreated historical controls and was found out to be safe.[22,26,29] In this review, treatment was initiated to thirteen patients below age 3 years old, even as early as 3 months old. Those with OI Type III were able to walk independently at age 3 years, while those with OI Type IV were able to walk at about 1.6 years of age.

Numerous research on the use of pamidronate in children have shown an increase in bone mineral density compared to baseline using bone densitometry or DEXA in the lumbar spine.[3,26,27,32-34] This is a good parameter to monitor efficacy of treatment. However, in a developing country, the cost is prohibitive. Studies by Glorieux et al.[17] and Abacan et al.[10] used the metacarpal index instead to approximate the bone mineral density revealing an improvement in the patient's osteopenia after treatment. Measurement of metacarpal index to approximate BMD may be included to objectively measure outcomes in the future.

The UP-PGH Bisphosphonate Treatment Program for OI is sustained with donations coursed through the Philippine Society of Orphan Diseases. Even with free medicine, some patients, not included in this study, are not able to comply with treatment. The distance and difficulty in traveling due to mobility issues hinder patients to avail of the treatment as well as the holistic care they need. Furthermore, as a rare, heterogeneous group of disorder with a wide spectrum of clinical presentation, awareness and recognition of the disease

among health care practitioners outside tertiary centers need much improvement.

With an estimate of about 90 known OI patients in the database of the Division of Clinical Genetics, a collaborative patient health registry, specifically for Filipino OI patients, is recommended to provide sufficient data that will facilitate a better understanding of this condition. The collection of standardized data to monitor outcomes and study best local practices in care or treatment will improve patient care, and support healthcare management.[35,36] A formalized OI Registry may serve to describe the clinical history and course of the disease among Filipino patients, to determine response to treatment and safety of pharmacologic, surgical, and rehabilitative interventions, to measure quality of care, and to encourage further research about OI. More comprehensive and standardized tools are vital to better assess clinical outcomes by health professionals and to be able to communicate effectively to the families using this common language.

The presence of rare diseases such as OI in the country warrants attention from the health care administration in the country. Rare diseases need to be recognized to contribute significant morbidity and mortality, whose impact is not only to the families but also to the society. The National Rare Disease Act passed in March 2016[37] specified the formulation of a comprehensive and sustainable health system for orphan or rare disorders such as OI. Its successful implementation is anticipated to help improve the access to care and improve the overall quality of life of these patients.

Limitations of the Study

The data gathered in this retrospective study were from the available medical records for review. The retrospective nature of the study risks missing data due to incomplete documentation. Also, because of the small sample size, subgroup analysis by OI type was not done.

CONCLUSION

This study adds to the evidence that early intravenous pamidronate treatment in young children with moderate-to-severe OI is well-tolerated and associated with reduced fracture frequency and improved gross functional mobility.

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All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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REFERENCES

1. Alharbi SA. A systematic overview of osteogenesis imperfecta. Mol Biol. 2016;5(1):1-9. doi:10.4172/2168-9547.1000150.
2. Morello R, Esposito PW. Osteogenesis Imperfecta. In: Lin Y. Osteogenesis, 1st ed. Croatia: InTech; 2012. pp. 223-252.
3. Rauch F, Glorieux FH. Osteogenesis imperfecta. Lancet. 2004 Apr;363(9418):1377-85. doi: 10.1016/S0140-6736(04)16051-0. PMID: 15110498.
4. van Dijk FS, Cobben JM, Kariminejad A, Maugeri A, Nikkels PG, van Rijn RR, et al. Osteogenesis imperfecta: a review with clinical examples. Molecular syndromology. 2011 Dec;2(1):1-20. doi: 10.1159/000332228. PMID: 22570641; PMCID: PMC3343766.
5. Baljet B. Aspects of the history of osteogenesis imperfecta (Vrolik's syndrome). Annals of Anatomy. 2002 Jan;184(1):1-7. doi: 10.1016/S0940-9602(02)80023-1. PMID: 11876477.
6. Sillence D, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. Journal of medical genetics. 1979 Apr 1;16(2):101-16. doi: 10.1136/jmg.16.2.101. PMID: 458828; PMCID: PMC1012733.
7. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. American journal of medical genetics Part A. 2014 Jun;164(6):1470-81. doi: 10.1002/ajmg.a.36545. PMID: 24715559; PMCID: PMC4314691.
8. Thomas IH, DiMeglio LA. Advances in the classification and treatment of osteogenesis imperfecta. Current osteoporosis reports. 2016 Feb;14:1-9. doi: 10.1007/s11914-016-0299-y. PMID: 26861807.
9. Marini JC, Forlino A, Bächinger HP, Bishop NJ, Byers PH, Paepe A, et al. Osteogenesis Imperfecta. Nat Rev Dis Primers. 2017 Aug 18;3:17052. doi: 10.1038/nrdp.2017.52. PMID: 28820180.
10. Abacan MA, Boquiren RA, Elepaño IV, Alcausin MM. Change in bone mineral density of Filipino patients with Osteogenesis Imperfecta after 6 months of pamidronate therapy in a tertiary hospital in the Philippines. Acta Med Philipp. 2015 Dec;49(4):7-11. doi: 10.47895/amp.v49i4.883.
11. Barnes AM, Chang W, Morello R, Cabral WA, Weis M, Eyre DR, et al. Deficiency of cartilage-associated protein in recessive lethal osteogenesis imperfecta. New England Journal of Medicine. 2006 Dec;355(26):2757-64. doi: 10.1056/NEJMoa063804. PMID: 17192541; PMCID: PMC7509984.
12. Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. American journal of medical genetics Part A. 2011 May;155(5):943-68. doi: 10.1002/ajmg.a.33909. PMID: 21438135, PMCID: PMC3166781.
13. Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, et al. Nosology of genetic skeletal disorders: 2023 revision. American Journal of Medical Genetics Part A. 2023 May;191(5):1164-209. doi: 10.1002/ajmg.a.63132. PMID: 36779427; PMCID: PMC10081954.
14. Alcausin MB, de Dios, JKL, Chiong MD, Cavan BCV, Padilla CP, Cutiongco-de la Paz EM. Intravenous pamidronate treatment in Filipino children with moderate to severe Osteogenesis Imperfecta. Acta Med Philipp. 2011 Oct;45(4):35-9. doi: 10.47895/amp.v45i4.4753.
15. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo clinic proceedings. 2008 Sep;83(9):1032-45. doi: 10.4065/83.9.1032. PMID: 18775204; PMCID: PMC2667901.
16. Russell RG. Bisphosphonates: mode of action and pharmacology. Pediatrics. 2007 March;119 Suppl 2:S150-62. doi:10.1542/peds.2006-2023H. PMID: 17332236.
17. 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 Oct;339(14):947-52. doi: 10.1056/NEJM199810013391402. PMID: 9753709.

18. Plotkin H, Rauch F, Bishop NJ, Montpetit K, Ruck-Gibis J, Travers R, et al. Pamidronate treatment of severe Osteogenesis Imperfecta in Children under 3 Years of Age. J Clin Endocrinol Metab. 2000 May;85(5):1846-50. doi: 10.1210/jcem.85.5.6584. PMID: 10843163.
19. DiMeglio LA, Ford L, McClintock C, Peacock M. Intravenous pamidronate treatment of children under 36 months of age with osteogenesis imperfecta. Bone. 2004 Nov;35(5):1038-45. doi: 10.1016/j.bone.2004.07.003. PMID: 15542028.
20. Vallo A, Rodriguez-Leyva F, Rodríguez Soriano J. Osteogenesis imperfecta: anthropometric, skeletal and mineral metabolic effects of long-term intravenous pamidronate therapy. Acta Paediatrica. 2006 Mar;95(3):332-9. doi:10.1111/j.1651-2227.2006.tb02235.x. PMID: 16497645.
21. Land C, Rauch F, Travers R, Glorieux FH. Osteogenesis imperfecta type VI in childhood and adolescence: effects of cyclical intravenous pamidronate treatment. Bone. 2007 Mar 1;40(3):638-44. doi: 10.1016/j.bone.2006.10.010. PMID: 17127117.
22. Åström E, Jorulf H, Söderhäll S. Intravenous pamidronate treatment of infants with severe osteogenesis imperfecta. Archives of disease in childhood. 2007 Apr 1;92(4):332-8. doi: 10.1136/adc.2006.096552. PMID: 17114205; PMCID: PMC2083683.
23. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39(4):214-23. doi: 10.1111/j.1469-8749.1997.tb07414.x. PMID: 9183258.
24. Ruck-Gibis, Plotkin H, Hanley J, Wood-Dauphinee S. Reliability of the gross motor function measure for children with Osteogenesis Imperfecta. Pediatric Physical Therapy. 2001;13(1):10–7. PMID: 17053645.
25. Giraud F, Meunier PJ. Effect of cyclical intravenous pamidronate therapy in children with osteogenesis imperfecta. Open-label study in seven patients. Joint Bone Spine. 2002; 69(5):486-90. doi: 10.1016/s1297-319x(02)00434-7. PMID: 12477233.
26. Alcausin MB, Briody J, Pacey V, Ault J, McQuade M, Bridge C, et al. Intravenous pamidronate treatment in children with moderate-to-severe osteogenesis imperfecta started under three years of age. Hormone research in paediatrics. 2013 May;79(6):333-40. doi: 10.1159/000351374. PMID: 23735642.
27. Gökşen D, Çoker M, Darcan S, Köse T, Kara S. Low-dose intravenous pamidronate treatment in osteogenesis imperfecta. Turk J Pediatr. 2006 Apr 1;48(2):124-9.
28. Senthilnathan S, Walker E, Bishop NJ. Two doses of pamidronate in infants with osteogenesis imperfecta. Archives of disease in childhood. 2008 May 1;93(5):398-400. doi: 10.1136/adc.2007.125468. PMID: 18089634.
29. Munns CF, Rauch F, Travers R, Glorieux FH. Effects of intravenous pamidronate treatment in infants with osteogenesis imperfecta: clinical and histomorphometric outcome. Journal of bone and mineral research. 2005 Jul 1;20(7):1235-43. doi: 10.1359/JBMR.050213. PMID: 15940378.
30. Marr C, Seasman A, Bishop N. Managing the patient with osteogenesis imperfecta: a multidisciplinary approach. J Multidiscip Healthc. April 2017;10:145–55. doi:10.2147/JMDH.S113483. PMID: 28435282; PMCID: PMC5388361.
31. Georgescu I, Vlad C, Gavriliu TȘ, Dan S, Pârvan AA. Surgical treatment in Osteogenesis Imperfecta–10 years experience. Journal of medicine and life. 2013 Jun;6(2):205. PMID: 23904885; PMCID: PMC3725451.
32. Lin HY, Lin SP, Chuang CK, Chen MR, Chang CY. Intravenous pamidronate therapy in Taiwanese patients with osteogenesis imperfecta. Pediatrics & Neonatology. 2008 Oct 1;49(5):161-5. doi: 10.1016/S1875-9572(09)60002-4. PMID: 19133566.
33. Shapiro JR, Thompson CB, Wu Y, Nunes M, Gillen C. Bone mineral density and fracture rate in response to intravenous and oral bisphosphonates in adult Osteogenesis Imperfecta. Calcif Tissue Int. 2010; 87(2):120-9. doi: 10.1007/s00223-010-9383-y. PMID: 20544187.
34. Kusumi K, Ayoob R, Bowden SA, Ingraham S, Mahan JD. Beneficial effects of intravenous pamidronate treatment in children with osteogenesis imperfecta under 24 months of age. Journal of bone and mineral metabolism. 2015 Sep;33:560-8. doi: 10.1007/s00774-014-0618-2. PMID: 25319557.
35. Heger M. A registry of registries? The US backs the idea for patients. Nature medicine. 2011 Jan;17(1):4. doi: 10.1038/nm0111-4a. PMID: 21217651.
36. Kodra Y, Weinbach J, Posada-de-la-Paz M, Coi A, Lemonnier L, van Enckevort D, et al. Recommendations for improving the quality of rare disease registries. Int J Environ Res Public Health. Aug 2018;15(8):1644. doi:10.3390/ijerph15081644. PMID: 30081484; PMCID: PMC6121483.
37. Republic of the Philippines. RA 10747. The Rare Diseases Act of the Philippines. Manila, Philippines. 2016 March. Retrieved from GovPH official gazette. 2016