Safety and Efficacy of Zoledronic Acid in children with Osteogenesis Imperfecta

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ABSTRACT

Objective: To evaluate the efficacy and safety of zoledronic acid in children with osteogenesis imperfecta (OI).

Study Design: Descriptive Study.

Place and Duration of Study: National Institute of Child Health, Department of Endocrine and Diabetes, Karachi, Pakistan, from January 2011 to December 2020.

Methodology: Children, with OI registered for the treatment, were included. Zoledronic acid was given to them by intravenous infusion over 30 minutes with a dose of 0.05 mg/Kg/day for a median duration of 60 (24-96) months. To ensure safety, patients were kept for 24 hours after dose administration to monitor any short-term side effects. The patients were assessed after every 3-6 months for frequency of fracture, bone pain, and BMD.

Result: Out of 82 children [40 females (48.8%) and 42 males (51.2%)], 11 patients (13.4%) had fever and 2 patients (2.4%) had flu-like illness. No other side effects were observed. The annual fracture rate decreased overall from 2.8±1.5 to 0.2±0.5 ($^{<}$0.001) in both males (2.6±1.3 to 0.1±0.4) and females (3.1±1.7 to 0.2±0.6). Z-score on DEXA scan showed improvement in BMD overall (-3.9±2.0 to 2.2 ±1.7), in males (-3.7±1.9 to -2.1±1.7) and in females (4.1±2.1 to -2.3±1.8). There were no other long-term side effects like ocular problems, osteonecrosis of the jaw, and delayed healing of the fractures.

Conclusion: Zoledronate use in children is associated with minimal short-term and long-term side effects with a significant improvement in BMD and decline in fracture rate.

Key Words: *Osteogenesis imperfecta (OI), Bisphosphonates (BPs), DEXA scan, Bone mineral density (BMD)*.

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INTRODUCTION

Osteogenesis imperfecta (OI) is an inherited connective tissue disorder with a wide clinical and genetic heterogeneity causing bone fragility.[1] Mutations in the collagen type I genes *COL1A1* (collagen type I, alpha 1) and *COL1A2* (collagen type I, alpha 2), which encode for α1 and α2 chains of type I collagen, respectively causing production of a defective collagen type I that leads to the significant reduction in bone mineral density which results in typical signs of OI that are; short stature, fragile bones, scoliosis, blue sclera, and dentinogenesis imperfecta.[2] Divided on the basis of clinical and radiological findings, severity of the disease, and molecular studies, almost 20 types have been noted uptil now with autosomal dominant, autosomal recessive, and X-linked recessive inheritance.[3]

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The estimated occurrence is about 1/10,000 and 1/25,000 globally. The incidence is about 1/10,000 or 1/20,000 live births in America; 5/100,000 live births in the Netherlands; 1/10,000 live births in Montreal Canada; and 1/20,000 live births in India.[3] In Pakistan, a total of 72 patients have been reported with the age range of 1-13 years.[4] Mutation G324C in *WNT1* (wingless) gene responsible for the recessively severe inherited OI, had been reported for the first time in Pakistan in 9 individuals of the same large consanguineous family.[5] Serine replacing glycine in the *COL1A1* gene was also reported locally at the National Institute of Child Health, in 2020.[6]

Till date, no single treatment has been defined for the patients with OI and multidisciplinary approach including physical therapy, orthopaedic procedures, and rehabilitation with avoidance of trauma had been the mainstay of the management. Among medical treatment, bisphosphonates (BPs), and the structural analogues of pyrophosphates had been used well for more than two decades in patients with osteogenesis imperfecta.[7,8] The second generation BPs Pamidronate, had been used worldwide as well as in local population with proven significant effects in OI children that includes enhanced bone mineral density (BMD), reduction in the rate of fracture and noticeable betterment in the functionality of the child.[4,9] Currently, Zoledro-

nate is considered to be the most efficient and safe BPs available. The osteoclastic activity gets inhibited by the use of bisphosphonate (BPs), and they are released into the bone matrix to bind with hydroxyapatite, and this leads to the effects of BPs to last for many years even when the drug is stopped. The recent evidence indicates that zoledronic acid not only inhibits osteoclast activity, but also exerts anabolic activity by stimulation of osteoblast differentiation.[9,10]

Zoledronate use in the paediatric age group has been documented for different indications globally, and the commonest short-term side effects are hypocalcemia and flu-like illness including fever, myalgia, and bone pain, but there is scanty data available in the local paediatric population.[8,9,11,12] The reported long-term side effects including ocular symptoms, delayed healing of the fractures, and osteopetrosis have always been a major safety concern for zoledornate's use. This study would help in the evaluation of long-term treatment response and short-term adverse effects in the local paediatric population and will also help in the follow-up studies in future. The aim of this study was to evaluate the efficacy and safety of zoledronic acid in children with osteogenesis imperfecta.

METHODOLOGY

A cross-sectional study of children aged 01 to 17 years, who were registered for the treatment of OI at the National Institute of Child Health, Department of Endocrine and Diabetes, between 2011 to 2020. Parents, who did not give informed consent, were excluded. The study protocol was approved and monitored by the local Medical Ethics Committee.

The diagnosis of OI was based on the presence of strong clinical history of the recurrent fractures, bone pain, and supported by the radiological examination and bone mineral density using a standard protocol dual-energy X-ray absorptiometry (DEXA) scan which shows the degree of osteoporosis in terms of Z-score. The baseline socio-demographic variables, number of the fractures, serum calcium, serum phosphorus, alkaline phosphatase, serum magnesium, serum albumin, serum vitamin-D, parathyroid hormone, and DEXA scan (bone mineral density) were recorded on a predesigned proforma by the primary investigator.

All the patients with OI received zoledronate dose of 0.05 mg/Kg intravenously over 30 minutes every six months for a minimum of 6 doses at least, and they were kept under medical observation for 24 hours each time to monitor the side effects like flu-like illness, myalgia, headache, fever, and symptomatic hypocalcaemia. Post zoledronate infusion, calcium, Vitamin D, and serum creatinine levels were measured to monitor the response and side effects of the treatment. To avoid hypocalcaemia, all the patients were kept on the supplementary doses of vitamin D and oral calcium according to their serum levels.

Patients were assessed, for number of fractures and bone pain, clinically by a senior paediatrician every 3-6 months. The annual fracture rate was recorded before and after zoledronate administration that was observed through radiographs. DEXA scans of lumbar spine and hipbone were done annually in all the cases to look for the improvement in BMD Z-score and recorded. Physical therapy and orthopedic intervention were offered to all as per need.

The data were processed by using Statistical Package for Social Science (SPSS). Frequencies and percentages were computed for the categorical variables like gender and age groups. Mean ± Standard Deviation was calculated for quantitative variables like number of the fractures and BMD score. Paired T-test was applied in the statistical analysis and p-value ≤0.05 was considered significant.

RESULTS

A total of 82 children with OI were analysed for short-term adverse events of zoledronate and beneficial effects on the number of fractures and bone mineral density after zoledronate therapy. The age range at the start of the treatment was 1-17 years. Eighty-two children with OI with an average age of (6.6 ± 4.8) years out of which 40 (48.8%) were under five years and the remaining 42 (51.2%) were above 6 years to the adolescent age group.

Among all, 42 (51.2%) were boys and 40 (48.8%) were girls. Overall the baseline biochemistry including calcium, phosphate, alkaline phosphatase, magnesium, albumin, and parathyroid hormone are presented in the mean standard deviation in Table I. Only 17 (20.7%) patients could have their bone turnover marker NTX done which was within the normal range (43.9 ±10.9).

Table I: Baseline characteristics.

Variable	Descriptive
Age (years)	6.0, 2.0-11.0
Age groups	
1 – 5 years	40 (48.8%)
6 – 17 years	42 (51.2%)
Gender	
Male	42 (51.2%)
Female	40 (48.8%)
Calcium (mg/dL)	9.6 ±0.8
Vitamin D (nmol/L)*	28, 18-38.3
Phosphate (mg/dL)	4.8 ±1.1
Alkaline Phosphate (IU/L)*	293.6 ±135.2
Magnesium (mmol/L)	2.1 ±0.3
Albumin (g/dL)	4.2 ±0.6
PTH (pg/mL)*	34.4, 18.2-55
NTX (nmol BCE)*~	43.9 ±10.9

*Categorical data is presented in frequency (percentage). Numerical data is presented in mean ±standard deviation. *skewed data presented in median, first quartile (25th percentile) – 3rd quartile (75th percentile). ~NTX data was available for n=17.*

The fracture rate decreased overall from 2.8±1.5 to 0.2±0.5 (<0.001) in both males (2.6±1.3 to 0.1 ±0.4) and females (3.1±1.7 to 0.2±0.6) per anum. There was significant reduction in fracture in both age groups *i.e.* in 1-5 years [from 2.0±1.1 to 0.8±0.3 (<0.001)] as well as in older children, 6-17 years [from 3.7±1.5 to 0.2±0.6 (<0.001)], which are both statistically significant.

Table II: Comparison of BMD scores and fracture numbers among the stratum of gender and age groups.

Variables	Pre-treatment		Post-treatment		95% CI of Mean difference	
	BMD [a]	Fracture rate [b]	BMD [a]	Fracture rate [b]	BMD [a]	Fracture rate [b]
Gender male (n=42)	-3.7 ±1.9	2.6 ±1.3	-2.1 ±1.7	0.1 ±0.4	-2.2 – -1.2	2.1 – 2.9
Gender female (n=40)	-4.1 ±2.1	3.1 ±1.7	-2.3 ±1.8	0.2 ±0.6	-2.2 – -1.3	2.4 – 3.4
Age under 5 (n=40)	-4.3 ±2.1	2.0 ±1.1	-2.2 ±1.9	0.8 ±0.3	-2.5 – -1.7	1.5 – 2.3
Age above 5 (n=42)	-3.5 ±1.9	3.7 ±1.5	-2.2 ±1.6	0.2 ±0.6	-1.9 – -0.9	3.0 – 3.8
Overall (n=82)	-3.9 ±2.0	2.8 ±1.5	-2.2 ±1.7	0.2 ±0.5	-2.1 – -1.1	2.4 – 3.0

*[a] Paired t-test was applied for p-value calculation. [b] Wilcoxon signed-rank test was applied. * p-value <0.05 was considered as statistical significant.*

Z-score on DEXA scan showed improvement in bone mineral density (BMD) overall from -3.9±2.0 to -2.2±1.7 (<0.001) in males (-3.7±1.9 to -2.1±1.7) and in females (-4.1± -2.1 to -2.3±1.8) by applying paired t-test. When compared between the age groups, BMD Z-scores were -4.3±2.1 to -2.2±1.9 in younger children (age 1-5) and -3.5±1.9 to 2.2±1.6 in older children (age 6-17 years) which was also significant (Table II).

None had a history of delayed fracture healing or nonunion during the study. No child had an episode of fracture after the first dose of zoledronate and with the subsequent doses. Fever was observed in 11 patients (13.41%), and 2 patients (2.4%) had flu-like reactions. Renal functions at quarterly intervals did not show any derangement after zoledronate exposure in the patients. Other side effects like ocular problems, osteonecrosis of the jaw, and delayed healing of fracture were also not observed.

DISCUSSION

The treatment of zoledronic acid is now well established and has been considered well tolerated. When zoledronate compared to oral alendronate, zoledronate was superior in reducing bone pain and increasing bone mineral density.[13] Zoledronate infusions in the real-world setting reduce pain and improve physical functioning in children with both mild and moderate-severe OI.[14] Multiple meta-analyses of RCTs proved that combining bisphosphonates with anabolic steroid therapy in the treatment of OI significantly improved the BMD at the total hip and femoral neck.[15,16]

This study depicts the 10-year experience of zoledronic acid use in children with osteogenesis imperfecta at the National Institute of Child Health, Karachi, Pakistan. The large size of the study group makes this research the first long-term observational clinical trial in an Asian population. A similar study has been reported by Kumar *et al*. with a lesser number of the subjects.[8]

The outcome of this study proved that the use of zoledronic acid intravenously is a potent treatment in paediatrics and adolescents with osteoporosis, as the target of medical therapy in this disease is to lessen the rate of fracture, reduction in bone pain, improved mobility, enhanced independence, and a decline in levels of bone turnover markers.

There was a significant reduction in fracture rate, and enhanced bone mineral density after zoledronic acid treatment as well as subjective improvement in bone pain in all the patients which was well comparable with the similar studies conducted in Saudia Arabia and India.[8,12]

A cross-sectional study corroborated that zoledronic acid significantly increased bone mineralisation (p<0.001) during the first year of treatment (p<0.001) when compared to other bisphosphonate therapy.[17] This also correlates with the results of enhanced bone mineral density in children treated with zoledronic acid during the first 6-12 months (p<0.001).

NTX level, which is a marker of bone turnover and reflects both osteoclastic and osteoblastic activities, was raised than normal at the start of ZA exposure similar to the previously reported cohort.[12]

Fever (38°C axillary temperature), and flu-like symptoms were observed in 11 (13.4%) and 2 (2.4%) patients, respectively after zoledronic acid infusion which were settled by an oral paracetamol similar to another study.[8]

Although Hogler *et al*. proved a noticeable hypocalcemia (74%) and hypophosphatemia (82%) after the first dose of zoledronate infusion, but the authors did not encounter an abrupt decrease in phosphate level and calcium level post zoledronate due to the regular supplementation of vitamin D and calcium.[18] This was also supported by a clinical study comparing the effect of zoledronate and alendronate in a cohort of 136 patients with OI.[13]

Though found in many relevant studies about the use of oral bisphosphonate and intravenous pamidronate, few unwanted effects on the gastrointestinal, renal, and ocular system did not observe in the study population.[19] Oral BPs use may have issues regarding compliance in children. Few studies have reported a few long-term side effects of delayed remodeling impaired longitudinal growth of bones, osteopetrosis, and occasionally sub-trochanteric fractures of the femur.[20,21]

Many authors have reported osteonecrosis of the jaw after zoledronate therapy similar to the current study indicating that it is not commonly found in children without contributing factors like periodontal disease or steroid usage.[8,22]

Concern regarding zoledronate long-term usage is that it gets absorbed into the bone and can stay there for decades.[23] A complete biochemical osteoporotic panel at the

end of the treatment remains the limitation of this study as well as the molecular genetic testing. Retrospective data collection is another limitation. The data strength is that we have done it on the maximum number of patients with different ages and presentations but the authors recommend more studies with forwarding data collection to get a better picture of BPs response in children with OI.

CONCLUSION

Zoledronate use in children with OI is associated with minimal short-term and long-term side effects with a significant improvement in bone mineral density and decline in fracture rate.

COMPETING INTEREST:
The authors declared no competing interest.

ETHICAL APPROVAL:
The Ethics Committee of the hospital provided approval for this study.

PATIENTS' CONSENT:
Informed consent was obtained from the patients to publish the data.

AUTHORS' CONTRIBUTION:
MR: Conception of study and article writing.
SH: Data entry, SPSS statistics, result, content typing and formatting.
MNI: Study design, methodology, and critical analysis of article.
ZAK: Data collection and proforma filling.
TML: Patient follow-up monitoring.
SJR: Critical analysis of the article.
All the authors have approved the final version of the manuscript to be published.

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