Original Article

Zoledronic Acid Treatment in Infants and Toddlers with Osteogenesis Imperfecta is Safe and Effective: A Tertiary Care Centre Experience

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Abstract

Context: Osteogenesis imperfecta (OI) is a genetic disorder of the extracellular matrix of bone characterized by low bone mass manifesting as frequent fractures, delayed motor development, pain, and impaired quality of life. The intravenous bisphosphonate, pamidronate is an established treatment for OI. Recently, zoledronic acid (ZA) has been used for the management of OI. **Aim:** To assess the efficacy and safety of ZA in children below five years of age with OI. **Settings and Design:** A hospital-based prospective observational study. **Methods and Material:** Patients with OI aged less than five years attending our centre were treated with intravenous ZA at a dose of 0.05 mg/kg every six months. Subjects were closely monitored for clinical and biochemical variables, adverse events, and new-onset fractures. The response to therapy was assessed by monitoring clinical variables including the degree of bony pains, number of fractures, height/length standard deviation score (SDS), and motor developmental milestones. All patients were analysed at baseline and at the end of two years for biochemical parameters and clinical severity score (CSS) as proposed by Aglan *et al*. with modifications. **Results:** After two years of treatment, OI patients showed a significant decline in the rate of fractures ($p < 0.001$), improvement in ambulation ($p = 0.005$), alleviation of pain ($p < 0.001$), and improvement in height SDS ($p < 0.05$). There was a significant improvement in CSS after two years of therapy. Apart from mild flu-like symptoms and mild asymptomatic hypocalcaemia immediately post-infusion, no other adverse effect was noted. **Conclusion:** ZA therapy in infants and children below five years of age with OI was effective and safe and a more convenient alternative to pamidronate.

Keywords: Clinical severity score, infants, osteogenesis imperfecta, zoledronic acid

Introduction

Osteogenesis imperfecta (OI) is a diverse group of inheritable skeletal disorders characterized by recurrent fractures and frequently compromised stature.[1]

Based on clinical features, Sillence *et al*.[2] in 1973 described four classical types of OI. Even though this classification system is widely accepted, it is rather subjective and based on the quantity of information that is accessible at a particular time. In a study done by Aglan *et al*.,[3] a scoring system was proposed for the quantitative evaluation of clinical severity in different types of OI, thus, providing a more refined sub-classification.

Cyclic intravenous therapy with bisphosphonates, particularly disodium pamidronate, is now the standard of care for the treatment of moderate-to-severe OI.[4] Zoledronic acid (ZA) is a third-generation bisphosphonate with superior potency, allowing the lesser frequency of administration that has been tried for several bone diseases, mainly in adults. The efficacy and safety of ZA in very young children with OI is lesser studied than in pamidronate.[5]

In the present study, we assessed the response to ZA treatment in infants and toddlers with OI in terms of the annual fracture

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rate, degree of bone pain, height/length standard deviation score (SDS), motor developmental milestones, and clinical severity score (CSS) before and after therapy. To the best of our knowledge, this is the first reported study using ZA therapy for OI in India in the below five years age group.

Subjects and Methods

This study was a prospective observational study conducted in the department of Endocrinology at our centre. Paediatric subjects with OI aged less than five years were included in this study after taking informed consent from their respective parents. The study was approved by the institutional ethical committee. The diagnosis of OI was made based on clinical manifestations including recurrent fractures, blue sclerae, dental abnormalities, and deafness complemented by radiological x-ray examination. Anthropometric measurements were taken and converted to age-sex-specific *z*-scores and SDSs for height/length and weight were calculated. Skeletal survey was done to assess radiological features and the number of fractures.

All the patients were treated with intravenous ZA every six months at a dose of 0.05 mg/kg/dose. For the patients who presented in the neonatal period, ZA was given from two months of age. In our study, ZA supplied under National Health Mission, manufactured by ADMAC Life Sciences was used, each vial of which contained 4 mg of the drug. The calculated dose was then diluted in 100 mL of 0.9 normal saline and was administered by slow intravenous infusion over a period of one hour under medical supervision. Before starting the infusion, calcium, phosphorus, albumin, alkaline phosphatase, vitamin D, iPTH, arterial blood gas, urine routine and calcium, electrolytes, complete blood count, creatinine, and liver function tests were done.

The patients were treated with vitamin D if they had vitamin D below 30 ng/mL before giving the infusion. The patients were given ZA only if they had vitamin D above 30 ng/mL and with normal calcium, creatinine, and liver function without any evidence of underlying infection. All subjects were started on calcium supplements prior to injection and patients were monitored for hypocalcaemia post-infusion and treated accordingly. The calcium and vitamin D intake was maintained as per the recommended daily allowances.

The patients received paracetamol (15 mg/kg/dose) for any post-infusion flu-like symptoms. The patients received orthopaedic intervention, physiotherapy, and rehabilitation treatment as per their clinical presentation and need. All patients were regularly followed up every three months, till the end of two years for clinical, biochemical parameters, and CSS as proposed by Aglan *et al*.[3]

The proposed scoring system incorporates five major criteria of high clinical significance: annual fracture rate, long bone deformities, motor milestones, length/height SDS, and bone mineral density (BMD). Each criterion is allocated a score from 1 to 4, and each patient was marked on a scale from 1 to 20 according to these five criteria.[3] [Table 1].

However, since BMD was not available in our hospital, it was excluded from the severity score. Also, as most of the children were having gross bony deformity with delayed motor developmental milestones, it was not practical to use the grading provided in CSS for follow-up. This was circumvented by using modification as suggested by Otaify *et al*.[6] where a score of one was used for improvement even if still delayed and a score of two for no improvement. After these modifications, the total score of CSS ranged from four to fourteen.

We also assessed the degree of improvement in pain by using the faces legs activity cry consolability (FLACC) scale. It is a practical, easy and validated tool for measuring the intensity of pain in pre-verbal children. This scale includes five parameters (FLACC), all of which are graded on a three-point scale for severity based on behavioural descriptions. Each indicator has a score ranging from zero to two giving a cumulative score of zero to ten.[7]

The statistical analysis was done using IBM Statistical Package for Social Sciences (SPSS) version 21.0. A P value <0.05 was considered statistically significant at a 5% level of significance. Frequency, percentage, and mean with standard deviation were used for quantitative data. For determining statistical significance between variables, paired student t test was used.

Ethical clearance statement

The study was approved by Gauhati Medical College & Hospital vide letter no. MC/190/2007/Pt-II/Dec-2021/31 on 10/01/2022. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures follow the guidelines laid down in the Declaration of Helsinki 2008.

Table 1: Proposed scoring system for osteogenesis imperfecta (Aglan *et al*.)[3]

Criterion points	1	2	3	4
Average no. of fractures per year	0-1	2-5	6-10	>11
Gross motor development	Normal	Delayed with catchup	Delayed with no catchup	Abnormal/arrested
Degree of long bone deformities±scoliosis	No deformity	Mild (noticed only by X-ray), no scoliosis	Moderate (noticed by both clinical examination & X rays affecting isolated long bones) +/− scoliosis	Severe (clearly visible by examination & affecting all long bones) + severe scoliosis
Height SDS	< −2.0	−2.1 to−3.0	−3.1 to −5.0	> −5.0
BMD (Z-score)	Normal	−1.5 to−1.9	−2.0 to −2.4	<−2.5

Results

This study included ten OI patients with an age range of 0.25 to 4.5 years. The male-to-female ratio was 4:6 and positive family history was present in four of the subjects. The baseline CSS was 9.9 ± 1.59. The baseline clinical and biochemical parameters of the study participants are shown in Tables 2 and 3, respectively.

At the end of two years of therapy with ZA, there was a statistically significant drop in the average annual fracture rate. There was a significant improvement in the degree of pain and gross motor development with improved ambulation at the end of the study duration. There was an improvement in height SDS which was statistically significant. There was a statistically significant decrease in the CSS with the ZA treatment. The comparison of clinical and biochemical parameters at the beginning of treatment and the end of the study is shown in Table 4. There was no significant difference in the biochemical parameters including serum calcium, phosphorus, and PTH except significant reduction in alkaline phosphatase and elevation in 25(OH) Vit D levels.

All patients had moderate to severe OI at presentation. Irrespective of the CSS at baseline, there was a consistent improvement in the degree of pain, new onset fracture, motor milestones, height SDS, and CSS. There was no difference in treatment outcome based on disease severity.

None of the subjects experienced any severe reaction to the treatment. Fever lasting for an initial one to two days was seen in 40% (4/10) of the subjects with the first infusion of ZA but did not recur with subsequent cycles. Biochemical hypocalcaemia without any clinical manifestations was seen in 20% (2/10) of the children after the first cycle of infusion but got corrected on subsequent visits on calcium supplementation.

Discussion

OI is a genetic disorder of the extracellular matrix of bone with a wide range of presentations. The chief defect in OI is in the production of collagen leading to poor bone quality with an increased risk of fragility. Extraskeletal manifestations of OI include blue sclerae, dentinogenesis imperfecta (DI), and a varying degree of deafness in later life. The clinical manifestations of OI present as a spectrum, with asymptomatic individuals having a slightly increased propensity for fractures, near-normal stature and life expectancy at one end, and recurrent fractures, severe bony deformities, gross stunting, mobility impairment to perinatal mortality at the other end.[1]

The majority of the cases of OI are transmitted in an autosomal dominant (AD) fashion caused by a mutation in either of the two genes encoding type 1 collagen, COL1A1 and COL1A2.[8] An AD variant of OI with interosseous membrane ossification, radial head dislocation, metaphyseal radiodense lines, and hypertrophic callus has been recently recognized and is caused by a 5′ UTR mutation of the IFITM5 gene.[9] Rare subtypes of OI with the autosomal-recessive inheritance pattern have been recognized and their molecular basis has been elucidated. A wide range of genes has been identified including CRTAP, FKBP10, SERPINH1, PPIB, SERPINF1, LEPRE1, BMP1, SP7/OSX, WNT1, and PLOD2.[9-13]

Based on clinical features, Sillence *et al*. in 1973 described four classical types of OI. Type I OI is the mildest form with normal or near-normal stature, nondeformed long bones and blue sclera with infrequent DI. OI type II is the most severe phenotype with fatality in the perinatal period. OI type III is the most severe phenotype compatible with life. These individuals have severely compromised stature, gross long bone deformities with impaired mobility, blue sclera and DI. OI type IV is a moderately severe phenotype with numerous fractures, variable short stature, mild to moderate bone deformities, normal sclera and without DI.[2]

The management of OI is multidisciplinary which includes bisphosphonate therapy, physiotherapy, orthopaedic surgery and rehabilitation. Bisphosphonates are a class of antiresorptive agents that act by inhibiting the function of osteoclasts. They were first used as a treatment in children with severe OI to improve bone fragility as early as 1987.[14] This treatment is being used extensively for over two decades in children and adolescents with moderate to severe OI and is now regarded

Table 2: Baseline clinical characteristics of study subjects

Serial Number	Age at Ist fracture	Age at diagnosis (in years)	DI	Blue sclerae	Deafness	Sillence classification	Family history
P1	3 yrs	4	-	-	-	Type 3	+
P2	Birth	3.58	-	+	-	Type 3	+
P3	Birth	0.25	+	-	-	Type 4	-
P4	6 months	2	-	+	-	Type 3	-
P5	20 days	0.4	-	+	-	Type 3	-
P6	1.6 yrs	4.5	-	-	-	Type 3	-
P7	3 months	2	-	+	-	Type 3	+
P8	1.4 yrs	3	-	-	-	Type 3	-
P9	2 yrs	4	-	-	-	Type 3	+
P10	1 yrs	2.66	+	-	-	Type 4	-

*DI: Dentinogenesis imperfecta

Table 3: Baseline biochemical parameters of study subjects

S Calcium (mg/dL)	S Phosphate (mg/dL)	25 (OH) Vit D (ng/mL)	PTH (pg/mL)	ALK P (IU/L)
9.5	5	17	68	174
9.6	5.2	28.9	35	323
9.2	5.3	39	28	216
10.3	4.7	42.1	25	234
9.8	5.5	13.63	39	189
9.9	5.1	22.3	35	308
10.1	5.6	33	18	160
9.6	4.8	38	20	188
8.4	8.6	8	75	317
10.1	4.2	35	12	168

Table 4: Comparison of clinical and biochemical parameters at baseline and end of 2 years follow-up

Parameter	Baseline (Mean±SD)	2 years follow up (Mean±SD)	*P*
S Calcium (mg/dL)	9.65±0.548	9.56±0.499	0.146
S Phosphate (mg/dL)	5.4±1.196	5.31±1.287	0.214
25(OH) Vit D (ng/mL)	27.693±11.802	60.3±11.518	<0.001
PTH (pg/mL)	35.5±20.801	27.5±7.397	0.170
ALK P (IU/L)	227.7±64.795	191.4±51.101	0.024
Annual Fracture Rate	6.1±2.33	0.8±1.03	<0.001
Gross Motor Development	1.9±0.31	1.3±0.48	0.005
Height SDS	−2.87±1.80	−2.43±1.77	0.048
Degree of Pain	7.6±0.96	1±1.05	<0.001
Clinical Severity Score	9.9±1.59	7.5±1.9	<0.001

as the cornerstone of medical management. Intravenous pamidronate is presently the most extensively employed medical therapy for children with moderate to severe OI, which is often administered in a cycle of 3 days at a frequency of every 2 to 4 months.[15] Intravenous bisphosphonate therapy is associated with improvements in bone pain, sense of well-being, linear growth and muscle strength, and vertebral and long bone mass as well as with a reduced fracture rate.

In a comparative study done by El Sobky *et al*.[16] in Egypt for the efficacy of combined pamidronate treatment and surgery as opposed to surgery alone in OI patients showed that the former approach was associated with better outcomes with a decreased rate of new fractures and an increase in BMD. There is a paucity of data on other intravenous bisphosphonates apart from pamidronate. ZA is a relatively new, heterocyclic nitrogen-containing intravenous bisphosphonate, that has been utilized in a handful of studies with varying protocols. Compared to pamidronate, ZA has superior potency, a long-lasting effect in suppressing bone turnover and more rapid intravenous infusion, allowing a lesser frequency of administration and more convenience. Presently data available for use of ZA in children with OI is scarce and variegated and an appropriate effective dosage has not been yet established. Although there are few studies from other countries using ZA in children with OI, this is the first reported study from India involving ten children with OI being treated with ZA and followed up for two years for the effect of this treatment. This present study confirmed the safety and efficacy of intravenous ZA in children with OI at a dose of 0.05 mg/kg and a frequency of every 6 months. In a study done by Brown and Zacharin from Australia, it was found that intermittent ZA infusions in patients with OI and related conditions previously treated with pamidronate was safe and effective. There was a decrease in the number of fractures and an increase in lumbar spine areal BMD and BMD z-score which continued to increase for up to 3.4 years after the commencement of ZA.[17] The adverse events were transient, noted only during infusion and more commonly associated with the first infusion.

In a study done by Vuorimies *et al*.[4] in Finland, intravenous ZA treatment in children and adolescents was associated with comparable treatment response to pamidronate with a more convenient infusion protocol. In another study done in Brazil by Barros ER *et al*.,[5] children with OI treated with ZA for one year had comparable clinical and BMD improvement with safety and efficacy similar to pamidronate. In another study done by Otaify *et al*.[6] from Egypt, six monthly infusions of ZA in patients with OI was associated with a significant increase in BMD Z-scores and a decrease in fracture rate.

In the present study, there was a significant decline in the degree of pain when followed from baseline to the end of the study period. There was also a significant improvement in motor milestones and ambulation. The existing literature reports a decrease in bone pain and an improved sense of well-being within weeks of commencement of bisphosphonate treatment.[18,19] This positive outcome might be a cumulative effect of decreased fracture rate and decreased pain with increased BMD. Concordant to our study, Otaify *et al*.[6] reported a significant reduction in the degree of pain with improved ambulation.

In our study, there was a significant improvement in height SDS from baseline to the end of 24 months of ZA infusion. Similar results were reported by Zeitlin *et al*. and Heino *et al*., where pamidronate treatment was associated with a significant improvement in height as early as at the end of 1 year.[20,21] In the study done by Brown and Zacharin and Barros *et al*. there was no effect on linear growth of ZA therapy.[5,17] In contrast, a study done by Otaify *et al*. showed a decrease in height/length SDS during the treatment period, which was statistically nonsignificant.[6] In another study done in neonatal-onset severe OI patients, cyclic pamidronate therapy started from a mean age of 2.8 months resulted in decreased height SDS during the treatment period.[22] These divergent results might be due to more proportion of severe OI patients in the later groups with multiple deformities of the long bones, kyphoscoliosis and multiple fractures.

The administration of the quantitative CSS as proposed by Aglan *et al*. with some modifications including as done by Otaify *et al*., to the studied subjects before the beginning of

therapy and at the end of two years post-treatment revealed a statistically significant decline in the degree of severity. The use of CSS is a useful tool for the assessment of treatment response in subjects with OI and hence is suggested to be used in all subjects with OI.

The most commonly encountered adverse event with ZA therapy in our cohort was transient flu-like reactions mainly fever. This infusion reaction was seen only with the first infusion in 40% (4/10) of the subjects and was not observed in subsequent cycles. The symptoms were largely self-limited and were controlled with conservative management such as antipyretics. This was similar to what has been described by other studies. Biochemical hypocalcaemia without any clinical manifestations was seen in two patients after the first cycle which got corrected on subsequent cycles. All subjects were using continuous calcium and vitamin D supplementation before and during intravenous ZA therapy. In a study done by Vuorimies *et al*.,[4] a transient decrease in serum calcium during infusion with ZA and was seen and two of the subjects developed symptomatic hypocalcaemia requiring intravenous calcium treatment.

Conclusion

ZA treatment in children with OI is safe and effective. Compared with pamidronate, the biannual infusion protocol of ZA infusion is more convenient. Smaller sample size, unavailability of BMD and genetic studies and lack of a control arm were potential limitations of this study. In fact, comparison with a parallel arm with the standard of care, pamidronate would have been more informative. However, there was limited availability of pamidronate at our centre along with the availability of ZA under the government scheme which was more cost effective. Further studies with larger sample sizes and longer periods of follow-up are required to establish optimal dosing, duration of treatment and long-term effects.

Key messages

Zoledronic acid was found to be a safe and effective treatment for OI in infants and toddlers with decreased fracture rate, improved ambulation and relief of pain.

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Conflicts of interest

There are no conflicts of interest.

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