REVIEW ARTICLE

The Role of Pamidronate in Pediatric Patients with Severe Osteogenesis Imperfecta

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Osteogenesis imperfecta (OI) is a heritable bone disorder with clinical features that include bone fragility, blue sclerae, and short stature. There are four main subtypes of OI, encompassing a wide range of clinical severity. The majority of patients have mutations in either the *COL1A1* or *COL1A2* gene that ultimately lead to an abnormal synthesis of or a decrease in the production of collagen. Bisphosphonates have been used effectively in adults and children to treat other bone disorders, since they have been proven to increase bone density through inhibition of bone resorption. Recent studies have demonstrated the advantages of pamidronate therapy in the treatment of children and adolescents with the more severe forms of OI. Pamidronate consistently increases bone mass, vertebral growth, and quality-of-life while decreasing the number of fractures in children with severe OI. Long-term effects are promising, and benefits of pamidronate therapy appear to outweigh the possible risks.

KEYWORDS: pamidronate, osteogenesis imperfecta, pediatrics

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ABBREVIATIONS: BMD, bone mineral density; COL1A1, proalpha1(I)-chain; COL1A2, proalpha2(I)-chain; hGH, Human growth hormone; NTX, N-telopeptide of type 1 collagen; OI, Osteogenesis imperfecta; Pi, serum inorganic phosphorus; PTH, parathyroid hormone; TRAcP, tartrate-resistant acid phosphatase; 25-OHD, 25-hydroxyvitamin D; 1,25-$(OH)_2$D, 1,25-dihydroxyvitamin

INTRODUCTION

Osteogenesis imperfecta (OI) is a congenital disorder caused by abnormal synthesis of collagen.[1,2] OI is classified into four distinct types depending on severity and clinical features and is characterized primarily by bone fragility, but clinical features can also include blue sclerae, short stature, skeletal deformities, and dental abnormalities. Children with OI were often mistaken for victims of abuse due to multiple or recurrent fractures.[3] However, as the awareness of OI has grown, so has the ability to differentiate between OI and child abuse. Very few treatment options are available to treat OI, and previously, medical treatment had not been very effective in altering the course of the disease, especially in those patients with severe forms of OI.[4] Recent studies have shown bisphosphonates to be beneficial by increasing bone mass in children with OI. This review focuses on the role of pamidronate, an aminobisphosphonate, in the treatment of the more severe forms of OI (primarily types I, III, and IV) in pediatric patients.

EPIDEMIOLOGY

OI occurs in all racial and ethnic groups. Its incidence in the United States is about one in 20,000 births, which includes children diagnosed up to 1 year of age.[3] This number does not include those children with milder forms of the disease that are not diagnosed until later in life; therefore, the incidence could theoretically be much higher than reported.

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CLASSIFICATION AND CLINICAL PRESENTATION

Sillence et al. developed the classification system for OI that is most commonly used today.[1,2] OI is divided into four subgroups depending on its clinical presentation (Table 1).[5] The severity of the disease can range from very mild to very severe. Type I is the most common form of OI and generally presents without any major deformities. Type II OI is always lethal in the perinatal period; therefore, studies pertaining to the treatment of this type of OI are not available. Children with types III and IV OI generally present with short stature, difficulty ambulating, and are more prone to deafness than those with type I; they also represent the group most commonly requiring medical and surgical treatment.

Since type IV OI includes patients who do not fit into any of the other categories, this group represents a heterogeneous group of patients.[6-9] Extensions of the current classification system were later proposed to include types V, VI, and VII; however, a universal classification system for these types has not been officially adopted due to the small number of patients afflicted. These patients were originally classified as having type IV OI, but they share unique characteristics that could distinguish them from other type IV patients. Types V and VI have clinical features different from patients with type IV and do not involve collagen type I mutations.[6,7] Type VII can be distinguished from the other types based on the fact that it is an autosomal recessive disorder localized on a chromosome different from the loci for collagen type I.[8,9] Other features of OI include increased bruising, hypercalciuria, nephrocalcinosis, skeletal fractures, scoliosis, ocular defects (keratoconus and retinal detachment), hydrocephalus, compression of the cervical spinal cord, peripheral weakness, and loss of bladder control.[1,2,5] Osteoporosis progresses with age. Bone mineral density (BMD) T-scores range from –2.5 to –4 at the proximal femur or lumbar spine by dual-energy x-ray absorptiometry (DEXA).[5]

ETIOLOGY

OI is caused by mutations in one of two genes, *COL1A1* and *COL1A2*, which code for the proalpha1(I)-chain and proalpha2(I)-chain, respectively, of procollagen type 1.[5] Procollagen type 1 is the precursor to collagen type 1, the major structural protein found in most connective tissues. Collagen type 1 is abundant in bone, tendon, and ligament, but it can also be found in the lungs, dentin, and sclerae.

OI presents as an autosomal dominant trait but sporadic mutations can also occur.[1,2,5] Mutations in the biosynthesis of collagen type 1 result in a decrease in the amount of collagen type 1 produced or an increase in the production of defective collagen.[4,10] In type IA OI, only the normal *COL1A1* allele is expressed. The mutant

Table 1. Classification of Osteogenesis Imperfecta[1-3,5]

TYPE	BONE FRAGILITY	CLINICAL FEATURES	SCLERAE
I (50%*)	Mild to moderate	IA Normal stature; onset of fractures after birth; no major skeletal deformities; presenile hearing loss; compression of posterior fossa in 10%; triangular facial shape with mandible narrowed anteriorly IB Similar to IA but with dentogenesis imperfecta; may be shorter in stature	Blue
II (5%*)	Very severe	Lethal in the perinatal period; multiple fractures at birth; severely deformed	Dark blue
III (20%*)	Moderate to severe	Extremely short stature; fractures at birth with progressive deformity; not usually ambulatory; severe osteoporosis; occasional deafness	White to blue
IV (25%*)	Mild to severe	IVA More severe than IA; variable stature; usually ambulatory but with mechanical support; patients who do not fit into any of the above categories; occasional deafness IVB More severe than IB; similar to IVA but with dentogenesis imperfecta	White to gray

** Frequency*

COL1A1 allele codes for premature termination codons but translation is stopped via a quality control process. The synthesis of collagen type 1 is reduced by approximately 50 percent, but otherwise normal proteins are produced. In the more severe forms of OI (types IB, II, III, and IV), expressed mutations in *COL1A1* or *COL1A2* give rise to a structural alteration of collagen type 1. The repeating amino acid sequence Gly–X –Y (where X and Y is any amino acid) of the triple helical domain of the collagen chain is often affected, most commonly by a substitution of the glycine component. Both types of mutations are detectable in approximately 80 to 90 percent of patients with OI.[10] The cause of OI in the remaining cases is unclear.

OI versus *CHILD ABUSE*

Victims of child abuse often present with skeletal fractures.[3] As many as 100,000 children under the age of five have been physically abused, approximately 30% of whom have presented with fractures.[11] For years, children with OI have been mistaken for victims of abuse; therefore, OI is now included in the differential diagnosis of child abuse. The two are distinguished from each other by characteristic physical features, family history, and fracture type. However, atypical findings may make it difficult to differentiate OI from abuse. Analysis of the synthesis of collagen from cultured dermal fibroblasts may be beneficial in identifying patients who could potentially have OI, even in milder forms of the disease. This test has been investigated as a means to distinguish cases of OI from suspected child abuse. One study found that many patients with other indicators of OI had normal collagen studies (15%) while a small percentage of patients with indicators suggesting abuse may present with abnormal collagen studies. Because of the implications associated with a false positive result (presumed OI when there may be abuse) or false negative result (presumed abuse), studies of collagen biosynthesis should only be conducted in those children whose physical and radiologic findings lead to an uncertain diagnosis. Once the diagnosis of OI is confirmed, the decision of what therapeutic option to pursue becomes very important.

TREATMENT WITH HUMAN GROWTH HORMONE

The pharmacotherapeutic options for OI are limited to very few drugs. Human growth hormone (hGH) is believed to increase collagen type 1 synthesis by stimulating the expression of insulin-like growth factor I and insulin-like growth factor binding protein-3.[12] Treatment with hGH may be beneficial in increasing bone density and growth velocity in children with mild type I disease. However, there is a possibility that the use of hGH in some patients may be associated with an increased risk of fractures.[13] Thus, alternate therapy may be needed to help those with more severe forms of OI.

MECHANISM OF ACTION AND SIDE EFFECTS OF BISPHOSPHONATES

Bisphosphonates have been used extensively to increase bone density and decrease bone resorption in adults, and are used to treat conditions such as osteoporosis and Paget's disease.[14] Currently, the only FDA-approved indications for pamidronate are for the treatment of hypercalcemia of malignancy, osteolytic bone metastases of breast cancer, osteolytic lesions in multiple myeloma, and moderate to severe Paget's disease of bone.[15] While not FDA-approved for use in children, these compounds have also been used in pediatric patients to treat a number of other disorders with good results (Table 2).[16]

Bisphosphonates work by inhibiting normal and abnormal bone resorption. Bisphosphonates can be broken down into two groups —those that do not contain nitrogen (e.g., etidronate and clodronate) and those that do (e.g., alendronate, risedronate, and pamidronate).[17] The mechanism of action for the non-nitrogen containing bisphosphonates is believed to involve the production of toxic analogs of adenosine triphosphate that lead to osteoclast apoptosis. Alternatively, nitrogen-containing bisphospho-nates inhibit the synthesis of farnesyl pyrophosphate in the mevalonate pathway.[17,18] This potentially leads to the inhibition of protein isoprenylation, resulting in osteoclast apoptosis and inhibition of osteoclast-mediated bone resorption. However, since some studies suggest that osteoclast apoptosis does not occur, this aspect of the

mechanism of action remains controversial.[19]

An "acute-phase reaction" is commonly seen during the first cycle of intravenous bisphosphonate therapy.[20] This reaction presents with an increase in body temperature and bone pain, but it does not seem to recur with subsequent infusions. Nausea and vomiting may also occur;[15,21] some patients may benefit from pretreatment with ondansetron.[22]

USE OF PAMIDRONATE IN OI

Several studies have demonstrated the advantages of using bisphosphonates in children and adolescents with OI, especially those afflicted with deforming types (types III and IV, and severe cases of type I). Glorieux et al. conducted a non-controlled, observational study that followed 30 children, ages three to 16 years (mean±SD; 9±4years), with severe OI (type III and IV).[20] Pamidronate (mean±SD; 6.8±1.1 mg/kg/year) was administered over three successive days by slow, intravenous infusion at four to six month intervals for 1.3 to 5.0 years (mean=765 days).

Bone density, measured by DEXA of the lumbar spine, increased significantly by a mean of 41.9±29%.[20] The z-score, which corrects bone density measurements for age, improved from –5.3±1.2 to –3.4±1.5 (P<0.001). Cortical width of the metacarpals increased significantly compared to pretreatment values and persisted for up to two years of treatment. The number of fractures decreased significantly (2.3±2.2 to 0.6±0.5 per year, P<0.001). Alkaline phosphatase, a measure of bone resorption and formation, decreased slightly but significantly from baseline (mean±SD; 13±8 %/year) while N-telopeptide of type 1 collagen (NTX), a marker of bone resorption, decreased to a greater degree (26±17 percent per year; P<0.001). The mean growth rates of the ten prepubertal children and the eleven children undergoing puberty increased following treatment but results were not statistically significant (P=0.16 and P=0.11, respectively). Pain and ambulation also showed improvement after pamidronate therapy but results were considered to be fairly subjective. An acute-phase reaction was seen in 26 of the patients but this reaction did not recur with repeated infusions. Although the study was non-controlled, the improvements seen in the patients were believed to be due to pamidronate therapy. However, long-term effects and the limits to the benefits of therapy are still unknown.

The previous study was extended to include children <3 years of age.[23] Nine patients ranging in age from 2.3 to 20.7 months (mean±SD; 10.7±4.5 months) with severe OI (type III and IV) were initially given pamidronate every four months. However, since infants experience a more rapid bone turnover and growth compared to older patients, the interval between treatments was decreased to six to eight weeks. Pamidronate was administered in a manner similar to the previous trial with cumulative doses averaging 12.4 mg/kg/year. The results were compared with six historical controls that also had severe OI but received no pamidronate therapy.

Where BMD z-score increased in the pamidronate group, a significant decrease in BMD was observed in the control group (P=0.02).[23] Other similar benefits to the previous study included decreased pain and improve-

Table 2. Indications for the Use of Bisphosphonates in Children[16]

Fibrodysplasia ossificans	Myositis ossificans
Fibrous dysplasia	Oxalosis
Gaucher type 3	Antenatal pamidronate for maternal hypercalcemia
Hypercalcemia	Familial idiopathic hyperphosphatasia
Idiopathic infantile aortic calcifications	Juvenile chronic arthritis
Juvenile osteoporosis	Calcinosis of dermatomyositis
Osteogenesis imperfecta	Congenital neutropenia treated with GCSF
Osteopenia (cerebral palsy, paraplegia)	Steroid-induced osteoporosis

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ments from baseline in vertebral area and fracture rate (2.6±2.5 vs. 6.3±1.6 per year in controls, P< 0.01) following 12 months of therapy. Side effects included transient hypocalcemia and hyperparathyroidism but the clinical significance of this remains unclear. Overall, children between 2 and 20 months of age with severe OI also experienced clinical and radiological improvements. However, the study did not evaluate the optimal length of treatment, and safety following long-term use remains undetermined.

In one of the few studies conducted in the United States, six children with OI received pamidronate according to the protocol described above by Glorieux et al.[24] When compared to baseline values, patients experienced a mean improvement in BMD of 48% with an average increase in z-score of 1 (range: 0.5–1.4, P<0.03). The number of fractures and the improvement in functional status could not be systematically evaluated due to the fact that increased mobility often led to more injuries. This study independently confirmed the results of Glorieux et al. that cyclic administration of pamidronate is beneficial in increasing BMD and physical activity.

Rauch et al. also analyzed the effects of pamidronate therapy on the bone tissue of children and adolescents with more severe forms of OI (types I, III, and IV) in order to determine the histological basis for the increase in BMD in these patients.[19] The study included 45 patients, ages 1.4 to 17.5 years (mean±SD; 8.4±4.3 years), who received pamidronate for one to four years. The dosing regimen was dependent on the age of the patient (Table 3). Iliac bone biopsies before and after approximately two years of treatment were obtained from alternate locations and then compared with those of two control groups: patients with OI who had not received any bisphosphonate therapy, and patients with no metabolic bone disease.

Patients experienced comparable increases in BMD and decreases in markers of bone resorption (NTX) compared to similar studies.[22] Cortical width increased by 88% (P< 0.001) and cancellous bone volume increased by 46% (P=0.006), representing an increase in trabecular number compared to pretreatment values.[19] Neither change was significantly associated with the duration of pamidronate therapy. Trabecular thickness did not significantly increase (P=0.10). An important delay in bone mineralization lag time was demonstrated compared to pretreatment values (P=0.002) and versus OI and healthy controls (P=0.002 and P=0.001, respectively). Overall, mineral apposition rate was not significantly different among any of the three groups, and osteoid thickness and percentage of bone surface actually decreased following pamidronate therapy. This is in contrast to what has been observed with the first generation bisphosphonate, etidronate.[17] The ratio of bone formation rate to bone surface decreased significantly in regions containing cancellous bone (P<0.001), indicating a decrease in cancellous bone remodeling.[19] Since remodeling does cause a transient structural weakness of bone tissue, a decrease in bone turnover may be beneficial. The long-term consequences of these structural changes on bone stability remain unclear. Therefore, these investigators recommended that cyclic administration of pamidronate in children with OI be used when clinical benefits outweigh potential long-term risks.

Microdamage in the tissue may accumulate over time, causing potential future problems. This was the case documented in a 12-year-old boy with pamidronate-induced osteopetrosis

Table 3. Pamidronate dosing schedule[19]

AGE* (yrs)	CYCLE LENGTH	CYCLE FREQUENCY	DOSE OF FIRST CYCLE (mg/kg/d)	DOSE OF SUBSEQUENT CYCLES (mg/kg/d)
< 2	3 days†	q 2 mo	Day 1=0.25 Days 2 and 3=0.5	0.5 for 3 days
2–3	3 days†	q 3 mo	Day 1=0.38 Days 2, 3=0.75	0.75 for 3 days
>3	3 days†	q 4 mo	Day 1=0.5 Days 2, 3=1	1 for 3 days

** all patients received adequate calcium and vitamin D intake according to the recommended daily allowance*
† consecutive days

(marble bone disease).[25] This patient did not have osteogenesis imperfecta, but had unexplained bone pain, fractures, idiopathic hyperphosphatasia, and thrombocytopenia. Following 2.75 years of treatment with pamidronate (>4 times the normal doses used in OI), this patient had evidence of osteopetrosis which included club-shaped metaphyses due to defective osteoclast activity, increased bone densiometry, elevated creatine kinase of the isoenzyme derived from bone cells (BB-CK), and elevated serum alkaline phosphatase (bone isoenzyme). Bone remodeling defects persisted in this patient for at least two years following the discontinuation of pamidronate therapy. Therefore, because of concerns related to impaired bone remodeling following large-dose pamidronate therapy, close monitoring of biochemical markers of bone remodeling is recommended in patients receiving long-term pamidronate therapy.

Rauch et al. also conducted another study of 165 patients (ages 2 weeks to 17.9 years) with severe OI (types I, III, and IV).[26] This study only focused on the effect of pamidronate on bone and mineral metabolism; it did not evaluate any beneficial effects that pamidronate may have on bone stability. The dosing regimen was identical to that of the authors' previous trial (Table 3). The study population was stratified into three groups according to age. The first group included children less than two years of age, the second group included children between the ages of two and three years, and the last group included children older than three years of age. Biochemical measurements included serum inorganic phosphorus (Pi), alkaline phosphatase, ionized calcium (Ca^{2+}), parathyroid hormone (PTH), tartrate-resistant acid phosphatase (TRAcP, an osteoclast enzyme), 25-hydroxyvitamin D (25-OHD), and 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D]. They also measured creatinine (uCr), calcium (uCa) and NTX urine concentrations.

During the first three days of pamidronate therapy, serum Pi and Ca^{2+} decreased significantly from baseline in all age groups.[26] The decrease in Ca^{2+} did not cause clinical signs or symptoms of hypocalcemia in any of the patients, and Ca^{2+} levels returned to pretreatment results before the second treatment cycle. PTH levels increased considerably and were still significantly above baseline before the second cycle in patients less than two years of age ($P<0.01$). Serum concentrations of 25-OHD did not change during the three days of therapy, whereas 1,25-$(OH)_2$D levels doubled but returned to pretreatment values before the start of the second cycle. Urine calcium decreased significantly and was undetectable in 54 patients (35%) on the third day of the infusion cycle. All age groups experienced a significant decrease in uCa/uCr ratio after three days of treatment. Patients over three years of age still had a uCa/uCr ratio significantly below baseline before the second cycle ($P<0.05$). All age groups had a decrease in uNTX/uCr ratio ($P<0.001$), which remained significantly lower than baseline in all age groups at the start of the next cycle. The decrease in TRAcP was only significant in the oldest age group ($P<0.001$). The decrease in alkaline phosphatase was significant in all age groups ($P<0.001$) and continued to be lower than baseline before the start of the second cycle.

A subgroup analysis evaluated long-term effects in 40 patients who had started pamidronate therapy between 3–18 years of age and who were treated for at least four years.[26] Serum Ca^{2+} values did not change significantly over four years, but serum Pi decreased with time ($P<0.05$). PTH increased after two years ($P<0.01$) but remained stable and within reference ranges for the next two years. Serum levels of 25-OHD increased after the first year of therapy ($P<0.001$) but decreased steadily thereafter, whereas 1,25-$(OH)_2$D levels did not change. The uCa/uCr ratio decreased after two years of therapy but then stabilized. The uNTX/uCr ratio decreased during the first year ($P<0.001$) and continued to decrease slowly over the next three years. Serum TRAcP increased during the first two years ($P<0.05$) but returned to baseline values. Alkaline phosphatase values continued to decline steadily throughout the entire treatment period.

The most significant short-term effect of pamidronate therapy is the decrease in serum Ca^{2+} levels.[26] The authors recommended that patients maintain an adequate calcium intake to prevent serious effects of hypocalcemia, especially during the first infusion cycle. However, long-term Ca^{2+} concentrations remained unchanged. Because the uNTX/uCr ratio continued to decrease with long-term treatment with pamidronate, caution must be used because the effects of chronically low bone turnover in children are still unknown.

Zeitlin et al. analyzed both short- and long-term effects of cyclic intraveneous pamidronate on height and weight in a large group of children with severe forms of OI types I, III, and IV.[27] Patients received pamidronate as described in the previous trials.[20,23] Of the 125 eligible patients (0.04–15.6 years of age at baseline), 116 children were evaluated after one year of therapy and 41 children were evaluated after four years.[27] Rather than comparing patients with OI to healthy controls, the researchers used a regression analysis to determine the expected heights and weights for untreated patients with OI. Although there were few statistically significant changes in healthy population-based z-scores for height and weight in patients with OI (P=0.04, OI type III height only, P=0.01, OI type I weight only), all results were statistically significant (P<0.02) for height and weight when the percent change based on expected values were compared to baseline values after four years.[27] The only exception to this was the percent change in weight after four years for patients with OI type IV (P=0.05). An additional eight patients who achieved their final adult height during the study period also experienced a significant change in expected height compared to baseline when compared to predictions based on untreated patients (P=0.04). In conclusion, long-term cyclic pamidronate therapy has beneficial effects on height and weight based on expected growth patterns in untreated patients with similar types of OI.

Zacharin et al. conducted an open, observational study of 18 children (1.4–14.5 years) with types III and IV OI over a two year period.[28] This study not only investigated the effects of pamidronate, but it also evaluated the correlation between severity of the disease, age at onset of treatment, type of collagen mutation, and response to treatment. Similar to previous studies, treatment with pamidronate was effective in increasing BMD (124.7±75.7%) and vertebral height (68.5%) while decreasing the number of fractures. Although difficult to analyze statistically due to the heterogeneity of the population studied, all but two of the twelve patients with baseline disabilities who completed the studied experienced an increase in their mobility score (0 – bed or wheelchair bound, 4 – independent walking). All patients experienced a decrease in the number of fractures; however, the overall change in fracture rate could not be quantified. No significant correlation was found between the age at start of treatment and the response to treatment (r^2=0.14), most likely because the greatest benefits of pamidronate therapy on BMD were seen with the most severely affected patients. Side effects were minimal, although eight children experienced an acute-phase reaction. This study also found pamidronate to be safe and effective in treating children with severe OI, but long-term effects were not evaluated.

In one of the few long-term studies, 28 patients (0.6–18 years of age) with mild to severe OI received monthly infusions of pamidronate (10–40 mg/m^2) for two to nine years.[14] No adverse effects were noted with the exception of acute-phase reactions in five of the patients. The benefits of pamidronate therapy were consistent with findings from the other studies. Pamidronate may therefore be considered relatively safe and effective for long-term use for the treatment of OI.

Five separate case studies involving a total of 22 children have also concluded that cyclic pamidronate therapy is beneficial in patients with severe OI.[22,29-32] Nineteen patients received intravenous pamidronate in doses ranging from 2–14.4 mg/kg/year divided every six months to monthly, and three patients received 120–360 mg/m^2/year in monthly intervals. Two case series evaluated the benefits of oral pamidronate for the treatment of OI. One patient received oral pamidronate, 250 mg daily, for two months alternating with a two-month drug free interval.[33] Three boys (ages 1, 1.7 and 6 years) with OI type III received either 5 mg or 10 mg of oral olpadronate (a European name for pamidronate) per day.[34] All of the patients in these studies were treated for one to seven years. Significant increases in BMD, decreases in number of fractures and pain, and a relatively safe short-term side effect profile were consistently seen in each of the studies. There is a possibility that pamidronate is more effective in younger patients, but there is not enough data to support this since the study population was very small.[29] Also, the rate of fractures decreased less dramatically in one of the studies, possibly because the researchers used a dose smaller than previously studied.[34] The limited data available using oral pamidronate therapy suggest that patients unable to receive or tolerate parenteral therapy may

respond to oral therapy. Caution should be exercised, however, because the optimal oral dosing regimen has yet to be determined.

Other potential, yet unproven, benefits of pamidronate therapy include as increase in the success of surgical disease management.[28] In one study, surgeons reported decreased complications (delayed bone union, rod dislodgement) following intramedullary rodding in patients receiving pamidronate. Patients also reported less perioperative pain compared with previous procedures but this also has not been systematically evaluated.

SUMMARY

Children with the more severe forms of OI (mainly types III and IV) need prompt initiation of therapy to prevent further disabilities. Although treatment options are limited, the use of bisphosphonates such as pamidronate has proven to be beneficial. Pamidronate is recommended in children with severe OI because it has consistently been shown to increase bone mass, vertebral growth, mobility, and quality of life while decreasing the incidence of fractures. While there is a potential for impairment of bone remodeling when used at high doses, overall, long-term effects of pamidronate are promising, and the benefits of its use in children with moderate to severe disabling as a result of OI outweigh the possible risks.

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