The Role of Bisphosphonates in Pediatric Orthopaedics: What Do We Know After 50 Years?

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Abstract: The first described case of bisphosphonate use in a pediatric patient was 50 years ago, in 1969. Since then, bisphosphonates have been used for therapy in a wide variety of pediatric conditions, especially those of osteoporosis and bone fragility. Bisphosphonates have become standard medical therapy for moderate and severe osteogenesis imperfecta, with studies consistently showing improvements in bone mineral density. Despite the widespread use in this condition, there are no firm guidelines on treatment regimen or duration. Bisphosphonates have also been explored in the therapy of pediatric secondary osteoporosis. Although many studies have shown promising results, the evidence is not strong enough to inform clinical management conclusively. Clinical study of bisphosphonate use in avascular necrosis has not been as promising as the data from preclinical, animal model work. Although multiple studies have shown that bisphosphonate therapy improves pediatric bone mineral density, further study is needed to understand better the appropriate indications and treatment, as well as the clinical impact, including fracture reduction and effects on pain and quality of life.

Key Points:

- Bisphosphonates are accepted therapy for moderate and severe osteogenesis imperfecta. Studies consistently show improved bone mineral density, and many studies report decreased fracture risk.
- Small studies have shown improvements in bone mineral density in patients with secondary osteoporosis from cerebral palsy and with glucocorticoid-induced osteoporosis in Duchenne muscular dystrophy
- Clinical study of bisphosphonates for pediatric AVN of the hip is limited and does not currently support use to prevent femoral head deformity. Bisphosphonates may decrease pain in AVN.
- Short-term use of bisphosphonates is considered safe and well-tolerated in the pediatric population. Long-term effects of bisphosphonate use remain unknown.

Introduction

The biologic effects of bisphosphonates (BPs) were first described in the medical literature 50 years ago[1]. Prior to this, BPs were primarily used chemically as inhibitors of corrosion and as industrial complexing agents[1]. In 1969, Fleisch et al. described using BPs for a rat model of osteoporosis in *Nature*[2]. The first clinical use of BPs was a pediatric case report in *Lancet* in 1969, describing the treatment of a child with myositis ossificans progressiva[3]. Over the last 50 years, BPs have been used clinically within the pediatric population to treat a wide number of diagnoses, frequently addressing conditions of bone fragility, as well as avascular necrosis (AVN) and other underlying bone abnormalities. For adults, BPs

are now first-line agents in the treatment of osteoporosis in postmenopausal women and older men. Additionally, there is FDA-approval for use in adults with glucocorticoid-induced osteoporosis, hypercalcemia of malignancy, bone metastases and Paget disease[4]. BPs have not been approved by the Food and Drug Administration (FDA) in the treatment of any pediatric bone disorders. Research efforts continue to determine the utility, efficacy, and safety of BP therapy in children.

It is important to understand the basic action and pharmacology of BPs, at least in brief. BPs attach to bone with varying affinity through hydroxyapatite binding sites. When osteoclasts resorb and internalize BP-impregnated bone, the osteoclasts' biochemical processes are impeded. Examples of interrupted processes include interference with osteoclast ability to attach to the bone surface, impairment in the ability to form the ruffled border, and limited proton production[5]. Nitrogen-containing BPs inhibit the enzyme farnesyl pyrophosphate synthase, which is critical for post-translational modifications of small guanosine triphosphate (GTP)-binding proteins in osteoclasts, thereby blocking the ability of the osteoclast to attach to the surface of bone for resorption. Due to strong bone affinity, BPs are retained in bone for a prolonged period, with one study showing detectable bisphosphonate release up to 8 years after the discontinuation of pediatric BP therapy[6].

Because this class of medication inhibits bone resorption, BPs have been used to address low bone mineral density (BMD) and fracture risk in a variety of pediatric conditions, such as osteogenesis imperfecta (OI) and other causes of osteoporosis. There has also been use in conditions of pediatric AVN and other bone disorders. The purpose of this review is to summarize and synthesize the most current literature on the use of BPs within pediatric orthopaedics and related disorders, 50 years after initial use.

Bone Mineral Density and Fracture Prevention

In the growing skeleton, BP therapy increases cortical thickness by interfering with the bone modeling that typically happens during growth[7]. Therefore, the primary use of BPs in the pediatric population has been in the treatment of low BMD and to minimize fracture risk. Bone health is an important part of pediatric care, and pediatric bone fragility is relatively common. Poor bone health in children can have significant morbidity, including but not limited to pain, fractures, spine/long bone deformity, developmental delays, and reduced mobility. Additionally, while adult osteoporosis is often due to bone loss, pediatric osteoporosis is frequently due to inadequate bone development and can have lasting effects on bone quality[8]. Primary pediatric osteoporosis is often genetic, such as from OI, but there are a wide number of causes of secondary pediatric osteoporosis, which can be due to underlying medical conditions and/or treatments[8]. The most robust pediatric clinical literature on BP use is in the treatment of OI, though research into BP use for other conditions affecting bone health has intensified in recent years.

Osteogenesis Imperfecta

OI is a genetic connective tissue disorder involving a wide-ranging spectrum of bone fragility; mild forms of OI may have only a slight increase in childhood fractures or early osteoporosis, yet more severe forms can lead to numerous fractures, significant disability, and even perinatal death. OI was classified into 4 clinical types in the 1979 Sillence classification[9]. Numerous additional OI types have subsequently been described based on phenotype and in some cases, associated gene[10]. For communication purposes and clinical use, many clinicians still use the 4 Sillence types, often with the addition of Type V which has hyperplastic callus seen radiographically (Table 1[11]). Affected individuals primarily have abnormalities of type I collagen production, therefore demonstrating intrinsic alteration and weakening of connective tissues,

especially bone. The majority of patients have mutations in the genes COL1A1 or COL1A2, but multiple other genes have been implicated in the disease. Typically, OI management is multidisciplinary at specialized centers, often involving pediatricians, geneticists, endocrinologists, orthopaedic surgeons, physical therapists, and orthotists, among others.

OI Type	Severity	Inheritance	Locus or Gene	Phenotype
Type I	Non-deforming form	AD	COL1A1 COL1A2	• Blue sclerae • Adulthood hearing loss • Osseous fragility (variable) • Most of the fractures occur during the preschool years and are less common after puberty
Type II	Perinatal lethal form	AD, AR	COL1A1 COL1A2 CRTAP LEPRE1 PPIB	• Extremely severe osseous fragility • Frequent fractures, often apparent at birth
Type III	Progressively deforming type	AD, AR	COL1A1 COL1A2 CRTAP LEPRE1 PPIB SERPINH1 BMP1 FKBP10 PLOD2 SERPINF1 SP7 WNT1 TMEM38B CREB3L1 SEC24D	• Normal sclerae • Moderate to severe osseous fragility • Severe deformity of long bones and spine • Variable clinical phenotypes • Fractures may be present at birth • Short Stature
Type IV	Moderate form	AD, AR	COL1A1 COL1A2 CRTAP PPIB FKBP10 SERPINF1 WNT1 SP7	• Normal sclerae • Osseous fragility • Severe deformity of long bones and spine • Fractures present during childhood and decreases after puberty • Short stature
Type V		AD	IFITM5	• Normal sclerae • Mild to moderate short stature • Hyperplastic callus • Mineralized interosseous membrane

Table 1. *Clinical types of OI*
AD = autosomal dominant; AR=autosomal recessive. Adapted from Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet. 1979;16(2):101-16, and Bonafe L, Cormier-Daire V, Hall C, et al. Nosology and classification of genetic skeletal disorders: 2015 revision. Am J Med Genet A. 2015;167a(12):2869-92.

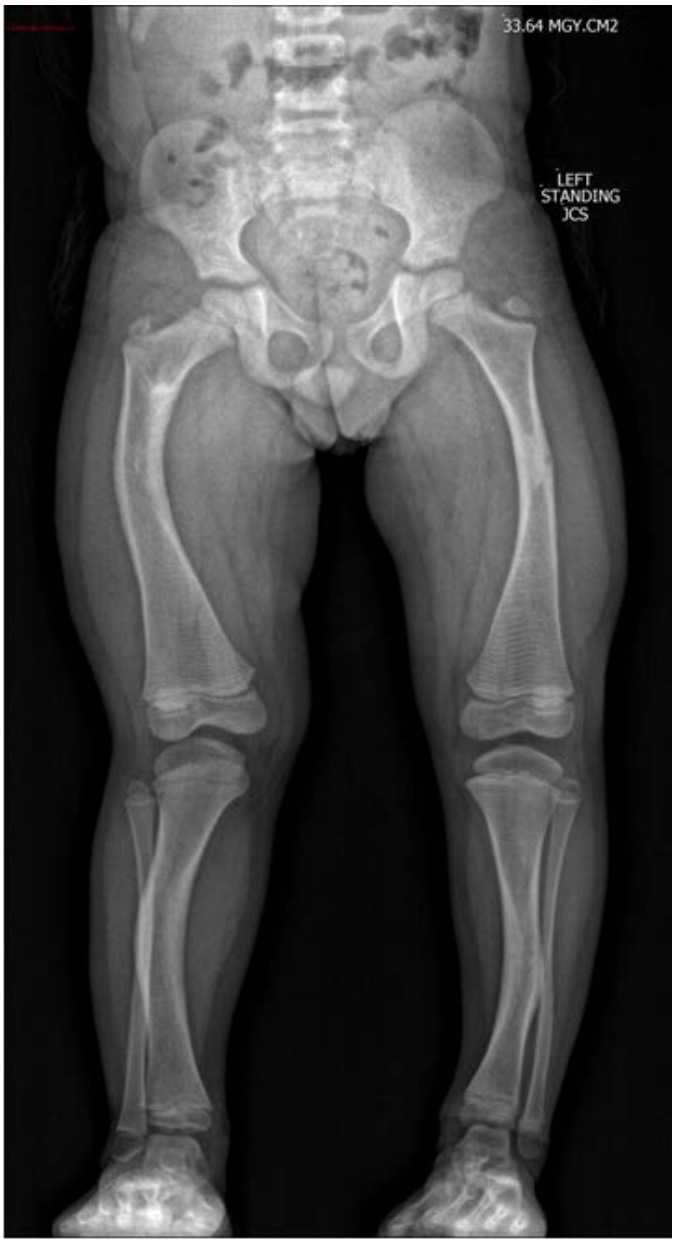

Figure 1. *Radiographic image of a 6-year-old boy with OI treated with BP therapy, demonstrating persistent bowing deformities of the long bones. Note classic radiographic striae or zebra lines.*

The first BP use in OI was reported in 1987[12]: a 12-year-old girl was treated with oral BP cyclically over the span of one year. Improvements in clinical and radiographic findings were noted, including the classic metaphyseal striae now commonly associated with BP treatment (Figure 1). Since that time, the use of BP therapy for pediatric OI has become widespread, yet there remains significant uncertainty in the literature with respect to the appropriate treatment regimen and overall clinical impact of BP therapy in children with OI.

There have been 3 recent systematic reviews of randomized controlled studies assessing the effects of BP therapy primarily in children with OI[13-15]. A Cochrane Database Systematic Review in 2016 included 14 randomized control trials in the treatment of OI with BP, including 12 pediatric studies[15]. All included studies reported statistically significant improvements in BMD after treatment with BP (either oral or intravenously), with multiple studies reporting the largest gains in BMD in the first year of treatment[16-22]. Beyond BMD findings, the systematic reviews found the literature to be less conclusive on other outcome measures, such as fracture reduction, pain, and quality of life[14-17]. Small patient numbers, heterogeneous patient populations, and a natural decrease in fracture rate with age make determinations of definitive therapy-related changes in fracture rate, in particular difficult.

Despite the conclusions made in the systematic reviews, it should be acknowledged that multiple independent studies reported improvements in fracture rate, pain, and quality of life measures following BP treatment. For example, Bishop et al.[17], in a multicenter, randomized, double-blind placebo-controlled trial of oral risedronate reported a significant reduction in fracture rate in the first year between groups (31% of risedronate treated group, versus 49% of placebo group, p=0.0446). They also noted reduced risk of recurrent clinical fractures in the BP treatment group. In another randomized double-blind placebo-controlled trial of oral BP therapy for children with OI, Sakkers et al.[23] reported a 31% reduction in long bone fracture relative risk with BP treatment, but no significant difference in functional outcome. In a more recent study of pediatric OI (types I, III and IV) treated with intravenous BP, Lindahl et al.[24] reported a significant decrease in non-vertebral fracture rate, compared to fracture rate prior to treatment, in all 3 OI types studied, with no demonstrated progression of vertebral compression fractures.

Although multiple studies reported a reduction in long bone fracture rate with BP therapy, long bone fractures remain a significant problem for children with OI. In a study of 37 children treated with intravenous BP therapy, patients had an average of 6 femur fractures and 5 tibia fractures during the mean 14.8-year follow-up period[25]. In a recent review, Trejo et al.[11] described several factors that contribute to heightened fracture risk that were not improved BP treatment. These factors include bone deformity, compromised material properties of the bone, and small diaphyseal cross-section of long bones.

In OI patients with vertebral compression fractures, treatment with intravenous BP has been reported to aid in the remodeling process of the compression deformity, showing improved vertebral shape[25-27]. While positive vertebral benefits were found with the use of intravenous BP, these findings have not been reproduced in studies of oral BP therapy. Two separate randomized trials using oral BP therapy versus placebo did not demonstrate an effect of therapy on vertebral fractures[17] or shape[22]. Although intravenous BP treatment has been shown to decrease scoliosis progression in certain OI types, BP treatment does not seem to affect the prevalence of scoliosis at maturity in patients with OI, nor does it translate to a decrease in ultimate progression to moderate or severe scoliosis[11,28,29].

The literature is inconclusive with respect to the effects of BP therapy on pain and quality of life[15]. Seikaly et al.[30], in a prospective, double-blind crossover study using oral BP and placebo, reported improvement in quality of life scores, such as self-care, well-being, and pain at one year in response to BP therapy. Other randomized studies have not reported a difference in pain[17-19,22.] For example, Ward et al.[22], found no difference in the percentage of patients reporting bone pain at 2-year follow-up in patients randomized to BP versus placebo. One recent study demonstrated improved parental perception of children's pain and quality of life immediately following infusion of zoledronic acid but did not find any significant perceived benefit in the patients themselves with respect to pain and quality of life[31]. Land et al.[32] reported improved mobility and ambulation level in children treated with intravenous pamidronate for 3 years compared to matched controls. Two smaller studies reported that treatment with intravenous BP correlated with improved functional mobility in OI patients, particularly when started at a young age[27,33].

There is currently a lack of standardization of bisphosphonate therapy regimen in children with OI. The literature describes variable dosing, administration routes, treatment schedules, and durations of treatment, and long-term effects of treatment remain unknown. There is only one study that directly compared outcomes with intravenous versus oral administration of BPs, reporting no difference between the groups in fracture incidence, BMD, or growth[34]. Despite this, many clinicians prefer intravenous BP therapy over oral therapy in the treatment of OI[35].

Adverse Events and Risks of Bisphosphonates in Osteogenesis Imperfecta

Although long-term studies are not yet available, BP therapy for pediatric OI for an intermediate period (1-3 years) appears to be safe[15]. Multiple studies report a flu-like reaction or acute-phase response, particularly after the first intravenous BP administration, but this is not unique to patients with OI[16,18,34]. Concern has also been expressed about the potential for delayed healing of fractures or osteotomies in children undergoing treatment with BP for OI; however, the literature remains inconclusive. One small study reported no significant delay in fracture healing[36], and another study reported delayed osteotomy healing but not fracture healing with intravenous BP treatment[37]. Holding BP therapy preoperatively is somewhat controversial, though recommendations have been made to delay BP therapy postoperatively until there is radiographic evidence of osteotomy healing[38]. Others have counseled that risk of pain and fracture may increase if BP therapy is discontinued after orthopaedic surgery[39].

The adult osteoporosis literature has reported risks with BP therapy, including atypical femur fractures (AFFs)[40] and jaw osteonecrosis[41]. The AFFs in adults are often low-energy, transverse subtrochanteric or diaphyseal femur fractures. Interestingly, this type of fracture is common in OI, and predates the use of BP therapy[42,43]. This fracture in OI has been attributed to collagen abnormality, altered mineralization and bone deformity[44]. Two recent retrospective studies have evaluated this fracture type in patients with OI, in patients with and without BP therapy[45,46]. Neither study found any relationship between this femur fracture type and BP therapy. In fact, both studies came to similar conclusions: that this AFF-like fracture pattern was associated with OI type or severity, not BP therapy. With respect to osteonecrosis of the jaw: this has not been reported in OI patients[15].

In summary, there is widespread use of BP therapy in the medical management of OI, and many consider BPs to be standard of care in moderate and severe OI forms. Although this treatment has received significant attention in the literature, the evidence does not definitively answer many of the important questions about this therapy, such as indications for treatment, appropriate dosing or administration route, and duration of therapy. BPs have reliably shown to increase BMD in OI, and there have been multiple promising reports of reduced fracture risk, though further work needs to be done to answer this conclusively. Short-term use is thought to be safe and well-tolerated, yet the long-term effects of this treatment remain unknown.

Secondary Osteoporosis

The current definition of pediatric and adolescent osteoporosis, whether primary or secondary, has been described by the International Society for Clinical Densitometry and includes the following features:

- One or more low-energy vertebral compression fractures
- In patients without vertebral compression fractures, the diagnosis is considered if there is significant fracture history (e.g. 2 or more long bone fractures prior to age 10, or 3 or more long bone fractures prior to age 19) and BMD Z-score of -2.0 or less[47].

It should be noted that the diagnosis of osteoporosis should *not* be made on BMD alone. In any pediatric patient with osteoporosis, the underlying cause and modifiable risk factors should be identified and addressed, if possible, before considering therapy such as BP. Although there are numerous causes of secondary osteoporosis in the pediatric population, this review will cover the current literature on osteoporosis-related to cerebral palsy (CP), Duchenne muscular dystrophy (DMD) and Rett syndrome.

Cerebral Palsy

The etiology of osteoporosis in patients with CP can be multifactorial, including limited mobility and weightbearing, negative effects of seizure medications, and nutrition. A 2012 systematic review[48] and a 2016 systematic review update[49] assessed the literature on the impact of weight bearing, BPs, and calcium and vitamin D on BMD and fracture risk in children with CP (GMFCS III-V). They reported evidence for BPs as "probably effective" in improving BMD and "possibly effective" in decreasing fracture rate[48,49]. They concluded that additional research would be beneficial. Due to the unknown long-term effects of BPs, the authors' subsequent clinical practice guidelines for bone health in CP recommended consideration of BP treatment only for patients being treated for fragility fractures and/or bone pain, not for prevention in CP patients at risk for osteoporosis[49].

Duchenne Muscular Dystrophy

Glucocorticoid treatment has become the standard of care in the treatment of DMD but has the unfortunate side effect of osteoporosis. A 2017 Cochrane review analyzed the literature pertaining to the effects of treatments for osteoporosis and fracture prevention in patients with DMD undergoing long-term corticosteroid therapy[50]. The review included two unpublished randomized clinical trials[51,52], only one of which assessed the effects of BP therapy in DMD. In

McSweeney et al.[51], 13 patients were randomized to risedronate, calcium and vitamin D, or to a group treated with calcium, and vitamin D alone. Significant improvement in BMD at 12 months was noted in those treated with risedronate compared to baseline. Other studies of BP therapy in DMD have been observational. One retrospective study showed a non-significant improvement in lumbar spine BMD in patients treated with alendronate compared to a non-BP group[53]. Another retrospective study showed improved spine BMD in those with DMD who started BP treatment at a younger age[54]. A more recent retrospective study of DMD boys on daily steroid therapy and prophylactic oral BP for one year demonstrated decreased rates of vertebral fracture compared to those in the untreated cohort[55]. Unfortunately, without good-quality randomized controlled trials to guide care, further study is clearly needed.

Rett Syndrome

In Rett syndrome, girls are at risk for low bone density and frequent fractures. One study showed that girls with Rett syndrome have a fracture incidence that is approximately 4 times the fracture incidence of the general population[56]. A retrospective study of 20 girls with Rett syndrome and bone fragility treated with intravenous BP for 2 years demonstrated decreased fracture incidence (compared to pre-treatment incidence), improved BMD of the spine, and 75% of parents reported improvements in their child's pain[57]. Clinical guidelines for bone health management in Rett syndrome suggest consideration of BP use in patients with vertebral fractures or clinically significant fractures with re-evaluation at one year, though the authors acknowledged a lack of evidence[58].

Although small retrospective series of BP therapy for secondary osteoporosis from CP, DMD and Rett syndrome have demonstrated early encouraging results, the evidence is not sufficient to guide practice or to definitively determine the effects of treatment. A significant additional prospective study will be needed to better understand the potential role and impact of BP therapy on secondary pediatric osteoporosis in these conditions.

Osteonecrosis

AVN of bone can lead to significant pain and morbidity in children and adolescents. The etiology is quite broad: AVN can be idiopathic, post-traumatic, iatrogenic, embolic, infection-related, medication-induced, or secondary to specific storage disorders (e.g. Gaucher's disease) or red blood cell disorders (e.g. sickle cell disease). There has been a particular focus in the orthopaedic literature on pediatric AVN of the femoral head due to the risk of significant pain, disability, and early degeneration of the hip joint. Studies investigating the potential role of BP therapy in AVN of the pediatric hip have included both pre-clinical animal models, as well as a limited number of clinical studies. Outside of the orthopaedic literature, studies have evaluated BP use for the treatment of chemotherapy-induced AVN.

Osteonecrosis of the juvenile femoral head leads to a general imbalance of bone resorption and formation, leading to a period of bone fragility and risk for femoral head deformation[59]. Both animal models of femoral head ischemia[60-62] and limited Legg-Calvé-Perthes disease histologic specimen[63] have demonstrated a pathologic remodeling process in which osteoclast-mediated resorption of necrotic bone predominates, and bone formation is relatively slow[59]. This results in a vulnerable environment in which the decrease in mechanical properties adjacent to weight-bearing articular surfaces may lead to femoral head damage and collapse[60-62]. The overarching goal of treatment in the setting of osteonecrosis is to maintain femoral head shape. The proposed role for BPs in the treatment of AVN would be to slow osteoclastic resorption, allowing time for revascularization and reossification upon the necrotic osseous framework, in an attempt to limit femoral head collapse.

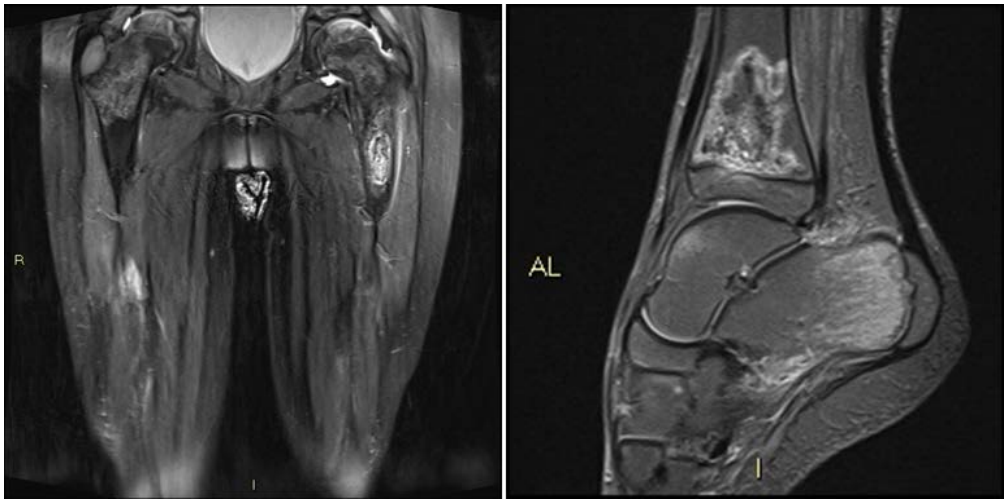

Figure 2. *Radiographic image of a 10-year-old girl with history of glucocorticoid treatment for ALL, with multifocal lower extremity pain. T2-weighted MRI images of bilateral femurs and left ankle show evidence of widespread osseous infarcts.*

Bisphosphonates in Animal Models of Osteonecrosis

Pre-clinical work has indicated beneficial effects of BPs on surgically induced femoral head ischemia in both juvenile rat[64] and piglet models[65], both considered animal models of Perthes disease. Improvements in femoral head architecture have been demonstrated in animals receiving intravenous bisphosphonates versus saline[64,65]. The delivery and distribution of intravenous BPs to necrotic bone is dependent on vascular perfusion, which is limited following ischemic necrosis of the femoral head[66]. Intraosseous injection of BPs directly into regions of necrotic bone have been studied in the piglet model and reported to be more efficacious in their distribution, retention, and impact[67]. In order to address both sides of the bone resorption/formation equation, complementary approaches of adding an anabolic agent, such as BMP-2, to the anti-resorptive BP therapy have been studied. Bone mineral content and mechanical properties both improved with the addition of BMP-2 vs. using BPs alone[68,69]. Concerns have been raised with this approach, however, due to subsequent formation of heterotopic ossification.

Clinical Use of Bisphosphonates for Osteonecrosis

Clinical information regarding BP use in pediatric osteonecrosis of the femoral head derives predominantly from adult studies[70-73]. Preliminary studies with intermediate follow-up showed reduced pain, improved function, and decreased rate of femoral head collapse[70,71,73,74]. However, subsequent prospective, multicenter randomized controlled trials demonstrated no significant difference in radiographic or patient-reported outcome measures in the treatment with either BP vs. placebo, or BP vs. no medication for adult AVN of the femoral head[72,75]. In fact, a recent meta-analysis of the efficacy of BP use in the treatment of femoral head AVN concluded that despite promising animal studies, adult clinical trials overall did not demonstrate better results in pain, amount of femoral head collapse, or need for arthroplasty[76].

Pediatric clinical study of BP therapy for femoral head AVN has been limited. Ramachandran et al.[77] evaluated a series of 17 patients with post-traumatic femoral head AVN as diagnosed on bone scan treated with intravenous BP therapy for a mean of 20 months. Good or excellent clinical outcomes were identified in all patients at mean 38 months of follow-up, and the majority of patients maintained good femoral head sphericity radiographically (i.e. 53% were Stulberg I or II), though no control group was included[77].

There is only one prospective randomized control trial of BP treatment for Legg-Calvé-Perthes disease[78]. Patients were randomized into 1 of 2 groups: standard of care treatment either with or without, intravenous BP therapy for 12 months. Preliminary findings presented at the 2019 Pediatric Orthopaedic Society of North America Annual Meeting, were: no significant improvement in

Deformity Index at 12-month or 24-month radiographic follow-up, though significant improvement in pain was noted at one year in the group treated with BPs, as well as improved hip range of motion[79]. There were no reports of fracture or jaw osteonecrosis.

BP Treatment in Medication-Induced Osteonecrosis

AVN, primarily in lower extremity joints, is a well-known complication of treatment for pediatric cancer. It is often associated with high dose glucocorticoid treatment in acute lymphoblastic leukemia (ALL, Figure 2), but AVN also affects patients with other malignancies treated with glucocorticoids. One study reported that 17% of pediatric ALL patients developed symptomatic AVN, and 72% had asymptomatic AVN as diagnosed on screening MRI[80]. Two small studies of BP therapy for ALL complicated by AVN reported decreased pain and improved musculoskeletal function[81,82], and 1 reported a decreased analgesic requirement[81]. One of the 2 studies reported on radiographic outcome and did not find a difference between the BP-treatment group and the control group[81]. The role of BPs in the treatment of chemotherapy-related AVN remains unclear.

Although animal studies have been promising, clinical studies to-date do not provide sufficient evidence to support the routine use of BPs for pediatric AVN for radiographic improvement or prevention of femoral head deformity. Preliminary clinical studies suggest that BP therapy may improve pain in children with AVN.

Bisphosphonates for Other Bone Pathologies

In addition to conditions of bone fragility and osteonecrosis, BPs have been used in a wide variety of other osseous pathologies and conditions. Examples include the treatment of bone pain in chronic recurrent multifocal osteomyelitis and fibrous dysplasia, treatment of Langerhans cell histiocytosis lesions, and management of ossifications in fibrodysplasia ossificans progressiva. Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory condition presenting as repeated flares of inflammatory bone pain at multiple foci with histologic signs of increased bone turnover. NSAIDs are generally accepted as a first-line medication for CRMO, and bisphosphonates have been considered for second-line treatment in patients who have persistent pain despite NSAID therapy. Studies of BP treatment for CRMO refractory to conventional NSAID treatment have been retrospective and include a small number of patients. Three studies of BP therapy in CRMO reported decreased bone pain[83-85], and 2 studies reported improved vertebral modeling in certain patients[84,85].

Fibrous dysplasia (FD), a rare skeletal condition in which fibro-osseous tissues replace normal bone and bone marrow, can lead to bone deformity, pain, and fragility. A randomized trial showed that treatment of FD with alendronate yielded a statistically significant reduction in bone resorption marker NTX-telopeptides and increase in areal bone mineral density in the lumbar spine in pediatric patients compared to the control group, though these findings were not statistically significant in the adults[86]. However, pain and functional parameters were not shown to improve with alendronate[86]. A number of smaller, observational studies have reported decreased pain with BP therapy for FD and did not find an effect on lesion size in children[87,88].

Langerhans cell histiocytosis (LCH) is a disorder of granuloma-forming immature immune cells, in which these granulomas are often in bone, causing pain, swelling, and increased risk of fracture. A retrospective nationwide survey in Japan reported 16 children with reactivated LCH who were treated with pamidronate[89]. In the intravenous BP treatment group, 75% of children had resolution of all active lesions (bone, skin, and soft tissue), and 50% of children had no active disease for a median of 3.3 years following treatment.

Fibrodysplasia ossificans progressiva (FOP) is a rare, disabling genetic connective tissue disorder involving progressive heterotopic ossification and episodic flare-ups[90,91]. BPs have been used for pain relief during flare-ups, especially when pain persists despite corticosteroid treatment. Kaplan, through personal observation,

reported decreased pain in approximately 75% of patients treated with BP for flare-up[92]. Due to the rarity of the condition, evidence on BP therapy in FOP is scarce.

Safety

Oral and intravenous BPs are typically safe and well-tolerated in the pediatric population. However, there is a lack of long-term efficacy and safety data; safety beyond ten years is not well-established. Many adverse effects seen in adults receiving bisphosphonates have not been found in children. These include increased risk of atrial[93], atypical femur fractures[40], osteonecrosis of the jaw[41], and orbital inflammation including uveitis and scleritis[94]. BPs cross the placenta, and there are potential teratogenic effects of gestational BP use such as low birth weight and transient neonatal hypocalcemia[95]. Since BP release has been reported up to 8 years after discontinuation of therapy, special consideration should be given when considering treatment of girls and young women[6].

Acute effects of pediatric intravenous BP treatment are relatively common and consist of a self-limiting acute phase reaction of mild fever, malaise, myalgias, and other flu-like symptoms for 1-2 days following the first infusion[38]. One study reported that 85% of children treated for a variety of bone disorders had this acute-phase response after the first dose of intravenous BP[96]. Acutely, patients may also develop transient hypocalcemia following intravenous BP treatment, especially after the first dose. This hypocalcemia is typically asymptomatic[97], but it is recommended that patients have appropriate calcium intake or supplementation and close clinical supervision[98].

Pediatric BP use can have long-term effects on bone development. During typical longitudinal growth, significant resorption occurs at the metaphyseal surfaces of long bones to maintain metaphyseal shape. BP therapy has been shown to interfere with this process, affecting distal femoral metaphyseal shape, though the clinical significance of this remains unclear[99].

Cumulative overdoses of bisphosphonates were shown to induce osteopetrosis, impaired bone modeling, and pathologic fractures in a single case report[100].

Conclusion

Over the last 50 years, bisphosphonates have been used in the treatment of a variety of pediatric bone conditions, primarily to address bone fragility, but also AVN and other bone pathologies. Most studies show that BP therapy improves BMD, and many studies report reduced fracture risk and decreased pain, though this evidence is less conclusive. In conditions such as pediatric AVN, fibrous dysplasia, CRMO, and FOP, small series have reported improvements in pain. There are currently no standardized treatment guidelines for agent, route, or dosage in pediatric bisphosphonate therapy. Long-term effects remain unknown; the benefits of treatment must be weighed with the potential risks given the lack of long-term studies. Further study is needed to understand further the appropriate indications, treatment regimen and clinical impact of this anti-resorptive therapy.

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