Evidence for Using Bisphosphonate to Treat Legg-Calvé-Perthes Disease

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Abstract

Background The rationale for using bisphosphonate (BP) therapy for Legg-Calvé-Perthes disease (LCPD) is the potential to prevent substantial femoral head deformity during the fragmentation phase by inhibiting osteoclastic bone resorption. However, it is unclear whether BP therapy decreases femoral head deformity.

Questions/purposes In this systematic review, we answered the following questions: (1) Does bisphosphonate (BP) therapy

decrease femoral head deformity and improve pain and function in LCPD or other juvenile osteonecrotic conditions? And (2) does BP therapy decrease femoral head deformity in experimental studies of juvenile femoral head osteonecrosis? **Methods** We searched the literature from 1966 to 2011 for clinical and experimental studies on BP therapy for juvenile femoral head osteonecrosis. Studies specifically addressing clinical and/or radiographic/histologic outcomes pertaining to pain and function and femoral head morphology were analyzed.

Results Three Level IV clinical studies met our inclusion criteria. Only one study initiated BP therapy during the precollapsed stage of osteonecrosis and reported prevention of femoral head deformity in nine of 17 patients. All studies noted subjective improvements of pain and gait in patients treated with intravenous BPs. Of the eight experimental studies reviewed, seven reported reduced femoral head deformity and six found better preservation of trabecular framework in animals treated with BPs.

Conclusions Clinical evidence lacks consistent patient groups and drug protocols to draw definitive conclusions that BP therapy can decrease femoral head deformity in juvenile osteonecrotic conditions. Experimental studies suggest BP therapy protects the infarcted femoral head from deformity, but it lacks bone anabolic effect. Further basic and clinical research are required to determine the potential role of BPs as a medical treatment for LCPD.

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Introduction

Legg-Calvé-Perthes disease (LCPD), or avascular necrosis of the capital epiphysis, was independently recognized as a distinct entity more than 100 years ago [6, 24, 36]. Two recent prospective multicenter studies [11, 47] and some

large retrospective studies [8, 15, 43] have provided valuable information regarding the femoral head deformity after current nonoperative and operative treatments. We have learned age at onset of disease and lateral pillar classification strongly predict radiographic outcome at skeletal maturity as defined by the degree of flattening of the femoral head. In children older than 6 years, only 43% of the patients had a spherical femoral head (Stulberg Class I or II outcome) at 5-year followup after a femoral varus osteotomy in a multicenter prospective cohort study [47]. In another multicenter prospective cohort study, Salter innominate osteotomy and femoral varus osteotomy produced spherical femoral heads (Stulberg Class I or II outcome) in 41% and 62% of the patients, respectively, at skeletal maturity [11]. The studies indicate current operative treatments, femoral varus osteotomy and Salter innominate osteotomy, do not reliably produce a spherical femoral head, especially for those children with onset of the disease after an age of 8 years.

Improved understanding of the pathophysiology of femoral head deformity after ischemic necrosis led to investigations of biologic agents to treat juvenile femoral head osteonecrosis. This approach targets the pathologic processes contributing to femoral head collapse, the imbalance of osteoclast-mediated resorption and delayed new bone formation (Fig. 1), as observed in histologic specimens of animal models of ischemic necrosis [16, 19, 39] and femoral head specimens from patients with LCPD

[9, 14]. In light of these findings, investigators have used bisphosphonates (BPs), antiresorptive agents, in experimental models of ischemic necrosis with the hypothesis that the inhibition of osteoclast-mediated resorption will preserve the trabecular framework of the necrotic femoral head, minimize deformity, and maintain the trabecular scaffold on which new bone formation can occur. While BPs reportedly decrease fracture risk and improve bone mineral density in postmenopausal osteoporosis [5, 27] and osteogenesis imperfecta [46], prevent bone complications in tumoral osteolysis [42], reduce hypercalcemia in childhood malignancies [30] and bone pain in fibrous dysplasia [23], and alter the aberrant bone turnover in Paget's disease [41], the use of BPs to prevent progression of deformity and improve symptoms in osteonecrosis is relatively novel. In adults with femoral head osteonecrosis, intermediate-term studies suggest BPs may have a role in reducing pain, increasing hip function, preventing further femoral head collapse, and delaying the need for joint arthroplasty [1, 2, 22, 33]. Clinical evidence to support the use of BPs in juvenile conditions of osteonecrosis is limited and worthy of critical appraisal.

The purpose of this systematic review was to determine whether BP therapy (1) decreases femoral head deformity and improves pain and function in LCPD or other juvenile osteonecrotic conditions and (2) protects the femoral head from collapse in experimental studies of femoral head ischemia.

Fig. 1A–B (A) A diagram represents normal bone remodeling where bone formation and resorption are equal. Because of equal bone anabolic and catabolic activities, there is no change in the bone mass. (B) A diagram represents pathologic bone remodeling observed after femoral head osteonecrosis. Increased bone catabolism and decreased bone anabolism produce a net bone loss and weakening of the femoral head.

Search Strategy and Criteria

We searched the MEDLINE, EMBASE, and Cochrane Library databases on July 7, 2011, for articles published between January 1966 and June 2011 using the following search terms: “(Perthes OR femoral head osteonecrosis OR ischemic necrosis femoral head) AND (bisphosphonate OR bisphosphonates)”. The search from each database identified 155, 79, and one article, respectively (Fig. 2). Because the searches identified articles on both adult and pediatric femoral head osteonecrosis, we further refined our search by limiting it to “all child (0–18 years)”, which identified 60, 10, and zero articles, respectively. To identify animal studies, the original search findings from the MEDLINE and EMBASE databases were limited to “animals”, which identified 21 and 15 articles, respectively. All citations were imported into EndNote® to eliminate duplicate articles, which left 67 clinical and 30 animal-related articles. The abstract of each article was reviewed by two of the authors (MLY, HKWK) for potential inclusion in the study. Full-text publications were obtained for relevant studies, and three reviewers (HKWK, DGL, MLY) independently assessed eligibility of the studies based on the defined

Fig. 2 A flow diagram demonstrates the method of article selection for clinical study inclusion.

inclusion criteria. All Level I to IV clinical studies reporting radiographic and/or clinical outcome of BP treatment in femoral head ischemia in the pediatric population (age 0–18 years) were included. Of the 67 clinical studies, we excluded studies on technetium-99 m phosphate (52), an analog of BP used for bone scintigraphy; studies using adult populations (four); a nonhuman study (one); a study of nonfemoral head osteonecrosis (one); a case report of fewer than five patients (one); and review articles (two). A total of 61 clinical articles were excluded based on these criteria, leaving six articles for full review by three reviewers (HKWK, DGL, MLY). Of these six articles, three did not address clinical or radiographic outcome of BP therapy and were excluded, leaving three articles for analysis [21, 32, 40].

Data were extracted by one reviewer (MLY) into pre-arranged summary tables. Items reviewed that may have influenced quality of the conclusions included study design, level of evidence, potential bias, aim of the study, prospective data collection, end point specific to study purpose, and loss to followup.

We applied the Methodological Index for Non-Randomized Studies (MINORS) [44] to judge the quality of the study conclusions (ideal maximum score is 16 for non-comparative and 24 for comparative studies). Demographic

data were detailed to expose the degree of heterogeneity in the population analyzed (Table 1). When reported, the staging system utilized to classify the degree of osteonecrosis was unclear so we did not attempt to combine results based on disease stage. The only consistent clinical outcome measure reported in each study was pain. Inconsistent reporting or lack of reporting of radiographic determinants of femoral head deformity created difficulty in collectively evaluating results. Therefore, we summarized the radiographic outcomes of each study. We defined failure as need for a surgical intervention including hip-preserving surgery or arthroplasty, which was reported in all studies and indicative of symptomatic and progressive femoral head collapse (Table 2).

We included experimental studies if animal models of femoral head osteonecrosis were used to investigate the effect of BP on femoral head bony architecture. Of the 30 animal-related studies, we excluded studies related to using technetium-99 m phosphate for bone scintigraphy (five), studies of nonfemoral head osteonecrosis (three), published abstracts from a meeting (two), review articles (two), an in vitro only study (one), and non-English articles (three) (Fig. 3). A total of 16 articles were excluded based on these criteria, leaving 14 articles for further review. Of the 14 articles, six articles were excluded due to a lack of

Table 1. Demographics for clinical studies evaluating bisphosphonate use in femoral head osteonecrosis

Study	Design/Level of evidence	Bias/MINORS score	Etiology of AVN	Detection of AVN	Stage AVN at diagnosis	Number of hips/patients	Average age (years)	Unique cohort features	Consecutive series	Average followup (months)	Followup	Years of investigation
Ramachandran et al. [40] (2007)	Prospective case series/IV	Selection/12	Traumatic	Technetium 99 m bone scans "cold"	Ficat I	17/17	12.7	Unstable SCFE Femoral neck fracture Hip dislocation	Yes	38.7 (25.6–58.3)	100%	2000–2003
Nguyen et al. [32] (2006)	Retrospective (prospectively collected) case series/IV	Selection/8	Malignancy Steroids Radiotherapy Chemotherapy	x-ray ± bone scan and MRI	1 (n = 1) 2 (n = 2) 3 (n = 3) 4 (n = 1)	7/6 (3 bilateral, 1 unilateral, 2 AVN of other joints)	14.3	ALL status post treatment protocol of high-dose steroids and chemotherapy	No	24	83%	Not stated
Kotecha et al. [21] (2010)	Prospective case series/IV	Selection/7	Malignancy Steroids Radiotherapy Chemotherapy	MRI	Severity determined by total volume of AVN lesion measured on MRI	29/17 (14 bilateral, 1 unilateral, 2 AVN of other joints)	13.5	ALL risk stratified to mild, moderate, severe groups to decide treatment (risk based on age, number of joints, severity of AVN lesion, pain, dysfunction, radiotherapy)	Yes	NA	NA	1994–2007

MINORS = Methodological Index for Non-Randomized Studies; AVN = avascular necrosis; SCFE = slipped capital femoral epiphysis; ALL = acute lymphocytic leukemia; NA = not available.

Table 2. Methodology and functional and radiographic outcomes reported from studies evaluating bisphosphonate use in femoral head osteonecrosis

Study	Bisphosphonate/ Dosage	Average duration of treatment (months)	Timing of treatment initiation	Additional treatment	Clinical outcome scores	Hip pain	Gait	Radiographic outcome	Prevention of femoral head collapse	Number of failures/ future surgery	Side effects	Limitations
Ramachandran et al. [40] (2007)	PAM: 1–1.5 mg/kg ZA: 0.025– 0.05 mg/kg	20.3 (7–39)	Within 3 months of traumatic event	Partial weightbearing Bone marrow injection	Harris hip score: 91.2 ± 11.2 (mean ± SD) Iowa hip rating: 92.1 ± 8.9 Global PODCI: 91.5 ± 8.3	14 of 17 improved	13 of 17 normal	Sulberg I/II: 9, III: 6, IV: 2 Ficat I: 8, II: 1, III: 8	9 of 17	4/flexion- valgus osteotomy	Acute phase response: 35 Hypocalcemia: 13	Bone scan detects femoral heads “at risk” for collapse
Nguyen et al. [32] (2006)	PAM: 1 mg/kg	24	Average 9.2 months (1–18) after diagnosis		None	4 of 6 improved at 12 months 3 of 6 improved at 24 months	4 of 6 improved mobility to independent walking at 12 months 3 of 6 maintaining function at 24 months	MRI x-ray	No MRI improvement at 24 months No new x-ray collapse at 12 months but 2 additional collapse at 24 months	3/THA (Stage I, II, and IV AVN at initiation of treatment)	Acute phase response	Small sample size Included collapsed patients AVN of multiple joints. Timing of treatment initiation variable
Kotecha et al. [21] (2010)	ALN: 70 mg/week PAM: 16– 65 mg/m ² PAM only: 5.3 (3–9)	ALN only: 15 (7–22) ALN + PAM: 17 (16–20) PAM only: 5.3 (3–9)	Average 9.4 months (0–29)	Conservative group treated with calcium + vitamin D and physical therapy only	None	Conservative: 7 of 8 no pain relief ALN: 3 of 6 persistent pain (crossed over to PAM with pain relief) PAM: 3 of 3 improved	Conservative: 7 of 8 reduced function ALN: 3 of 6 reduced function (crossed over to PAM group with improved function/ ROM) PAM: 3 of 3 improved function	NA	At least 4 progressed to collapse requiring additional surgery	2/THA and 2/planned THA (3 in conservative group and 1 in PAM group)	Gastrointestinal upset: 1	Nonuniformity of treatment protocol Poor followup (some patients still receiving treatment at conclusion of study)

PAM = pamidronate; ZA = zoledronic acid; ALN = alendronate; PODCI = Pediatric Outcomes Data Collection Instrument; NA = not available; AVN = avascular necrosis.

Fig. 3 A flow diagram demonstrates the method of article selection for experimental study inclusion.

parameters evaluating femoral head deformity (three) and nonfemoral head osteonecrosis (three). This left eight articles for full review by three reviewers (HKWK, DGL, MLY) [3, 12, 17, 28, 29, 34, 35, 45] (Fig. 3). The experimental studies were categorized based on animal model used to establish femoral head ischemia. As varying methods were employed to determine femoral head shape, radiographic and histologic results were summarized based on the criteria established in each study. Potential limitations of each study (in addition to the limited ability to extrapolate the data to humans) and methodologic flaws (including absence of control group or power analysis) were recorded (Table 3).

Results

We identified no randomized clinical trials pertaining to the research question concerning whether BP therapy decreases femoral head deformity and improves pain and function in LCPD or other juvenile osteonecrotic conditions. The current evidence is Level IV and limited to small case series and observational studies (Table 1). Of the articles reviewed, the etiology of childhood femoral head ischemia was

posttraumatic in one study [40] and high-dose corticosteroid/chemotherapy-induced after treatment for childhood leukemia or malignancy in two studies [21, 32]. All three studies were subject to selection bias. The two studies examining the patients with leukemia or malignancy had multisite osteonecrosis. In one of these studies, some patients received bone marrow injection in addition to intravenous BP therapy, which may have confounded the results. While BP therapy in children with LCPD has been reported [13, 31], no study addresses its effects on protecting the femoral head from collapse or minimizing patient symptoms of pain and impaired function. The drug protocols including dosage, timing of BP initiation, and duration of treatment were variable among studies and not standardized for patients with leukemia in the two studies (Table 2). The prospective series by Ramachandran et al. [40] was the only study initiating the administration of intravenous BPs within 3 months of diagnosing early-stage osteonecrosis in post-traumatic cases. Based on the Stulberg radiographic classification, deformity progression was prevented in nine of 17 patients in this study. The study, however, lacked a control group. In the studies examining the patients with leukemia or malignancy, a long-term radiographic benefit from BPs was not observed in three of six patients needing

Table 3. Summary of data reported in experimental studies evaluating the use of bisphosphonates in animal models of femoral head ischemia

Study	Animal model	Number of subjects	Control	Bisphosphonate/ Dosage	Drug delivery	Duration of treatment	End point	Power analysis	Radiographic outcome	Histologic outcome	Additional findings	Side effects	Limitations
Aya-Ay et al. [31] (2007)	Yorkshire piglet Femoral neck ligature	15 Saline: 5 280 µg IB: 5 560 µg IB: 5	Yes	IB: 280 and 560 µg (2.5% and 5% total systemic dose, respectively)	Intraosseous	Single dose 1 week post	8 weeks	No	Mean epiphyseal quotient IB higher	Trabecular bone volume and number better preserved in 560 µg IB	Drug widely distributed in femoral heads 48 hours postinjection with 50% and 30% drug retained 3 and 7 weeks postinjection, respectively	NA	Advanced disease process observed and a rapid weight gain over 8 week study period Added surgical trauma of second procedure
Little et al. [29] (2003)	Wistar rat Hip dislocation, division ligamentum teres, femoral neck soft tissue stripping	24 Saline: 8 ZA post: 8 ZA pre-post: 8	Yes	ZA: 0.1 mg/kg	Systemic SQ injection	ZA post: 1 and 4 weeks post ZA pre-post: above + 2 weeks pre	6 weeks	No	Mose circle analysis Saline: 71% aspherical ZA post: 13% aspherical ZA pre-post: 0% aspherical	Bone volume fraction and trabecular number reduced in saline compared to ZA Bone formation rate increased by 56% in saline over ZA	DXA-measured BMD reduced by 24% and 43% in femoral heads	NA	Model of traumatically induced femoral head AVN Unable to quantify amount of resorption or revascularization histologically
Kim et al. [17] (2005)	Yorkshire piglet Femoral neck ligature	24 Saline: 8 IB pre: 8 IB post: 8	Yes	IB: pre: total dose, 1.5 mg/kg; post: total dose, 0.8 mg/kg	Systemic SQ injection	IB post: 3x weekly x 6 weeks IB pre: above + 7, 5, 2 days pre Treatment began 1 week post	8 weeks	No	Mean epiphyseal quotient IB pre: 60% higher IB post: 40% higher	Trabecular bone volume IB pre: 100% greater IB post: 93% higher Trabecular number higher in IB Trabecular separation lower in IB	None	Femora 1.7 cm and 0.8 cm shorter in IB compared to saline	Drug dosing schedule not clinically realistic and dosage much greater than normal therapeutic range

Table 3. continued

Study	Animal model	Number of subjects	Control	Bisphosphonate/ Dosage	Drug delivery	Duration of treatment	End point	Power analysis	Radiographic outcome	Histologic outcome	Additional findings	Side effects	Limitations
Little et al. [28] (2005)	Rat Hypertension-induced spontaneous osteonecrosis	120 Saline: 40 ZA monthly: 40 ZA weekly: 40	Yes	ZA: total dose, 0.15 mg/kg	Systemic SQ injection	ZA monthly: 3 doses of 0.05 mg/kg ZA weekly: 10 doses of 0.015 mg/kg	15 weeks	Yes	Mean epiphyseal quotient ZA group higher Proportion flat heads Saline: 32% Weekly: 12% Monthly: 3%	Bone volume increased in ZA Bone formation rate reduced in ZA over saline	Ossification delay Saline: 53% ZA weekly: 10% ZA monthly: 21% Spontaneous osteonecrosis No difference among groups Saline: 53% ZA weekly: 65% ZA monthly: 52%	Femoral length reduced 2.6% in ZA weekly and 2.3% in ZA monthly compared to saline	Inability to detect which femoral heads suffered true ischemic insult (some heads may have complete recovery by 15 weeks)
Hofstaetter et al. [12] (2009)	New Zealand rabbits	60 Saline: 30 ALN: 30	Yes	ALN: 150 mg/kg/day	Systemic SQ injection	3 × weekly	6 and 12 months	NA	Bone volume fraction and BMD increased in ALN	NA	Reduction in articular cartilage degeneration based on Mankin score	NA	NA
Vandermeer et al. [45] (2011)	Yorkshire piglet Femoral neck ligature	16 Saline: 5 IB: 5 IB +BMP-2: 6	Yes	IB: 560 µg	Intraosseous	Single dose 1 week post	8 weeks	No	Mean epiphyseal quotient IB + BMP-2 group highest	Trabecular bone volume, thickness, number and osteoblast surface higher in IB + BMP-2 than in saline	Absence of necrotic bone in IB + BMP-2	Heterotopic ossification in IB + BMP2	Large doses of BMP used
Peled et al. [34] (2009)	Sprague-Dawley rat Division ligamentum teres, femoral neck soft tissue stripping	Control ALN	Yes	ALN: 200 mg/kg/dose	Systemic SQ injection	Daily x 6 weeks	6 weeks	NA	No femoral head distortion in ALN group	NA	None	NA	NA

Table 3. continued

Study	Animal model	Number of subjects	Control	Bisphosphonate/ Dosage	Drug delivery	Duration of treatment	End point	Power analysis	Radiographic outcome	Histologic outcome	Additional findings	Side effects	Limitations
Peled et al. [35] (2009)	Sprague-Dawley rat Division ligamentum teres, and femoral neck soft tissue stripping	20 Saline: 8 ALN: 12	Yes	ALN: 200 µg/kg/dose	Systemic SQ injection	Daily × 6 weeks	6 weeks	No	NA	Femoral head height/length ratios higher in ALN over saline and equivalent to nonoperative contralateral femoral head	None	NA	No estimation of percentage of necrotic bone or newly formed bone

IB = ibandronate; ZA = zoledronic acid; post = postoperative; pre-post: preoperative + postoperative; pre = preoperative; ALN = alendronate, SQ = subcutaneous; mean epiphyseal quotient = maximum epiphyseal height/maximum diameter; BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; AVN = avascular necrosis.

arthroplasty surgery, but enrollment included patients treated late when femoral head collapse was already present. Radiographic outcome was not clearly defined in one study with very short followup, but at least one of three patients required arthroplasty surgery due to progressive collapse. Combining all studies, consistent early (within 12 months) improvements in subjective pain and gait were observed in 24 of 29 patients receiving intravenous BPs.

The experimental studies looking at BP therapy of femoral head deformity consisted of both small-animal [28, 29, 34, 35] and large-animal [3, 12, 17, 45] models of femoral head ischemia (Table 3). In immature rats, the effects of zoledronic acid (the most potent aminobisphosphonate clinically available) were investigated in a surgically induced osteonecrosis model and in spontaneously hypertensive rats that develop a LCPD-like osteonecrosis. Greater trabecular bone volume and better preservation of femoral head shape were found in BP-treated animals compared to saline-treated animals (Fig. 4). Similar findings were obtained using a piglet model of surgically induced osteonecrosis after ibandronate therapy. BP therapy likewise protected the femoral head from deformity in mature rats [34, 35] and improved bone volume and mineral density in rabbits. One study investigated the effects of local intraosseous injection of BP into the infarcted femoral heads in immature pigs. The investigators found a wide distribution of the drug in the femoral heads and better preservation of the femoral head compared to saline-injected animals even with $\frac{1}{20}$ of a systemic dose. While trabecular bone preservation was observed with BP therapy, no new bone formation was observed in large-animal studies. A local intraosseous injection of BMP-2 along with BP (ibandronate) produced femoral heads with bony architecture equivalent to that of nonoperated controls in a piglet model of osteonecrosis, suggesting an additive bone anabolic effect by BMP-2.

Discussion

A recent multicenter prospective study showed poor radiographic outcomes in children of all ages with severe Lateral Pillar C LCPD, irrespective of nonsurgical or surgical treatment, warranting the investigation of novel therapies to prevent femoral head deformity [11]. A pathologic repair process marked by an imbalance of bone resorption and bone formation has been recognized as a major contributor to the pathogenesis of collapse in juvenile femoral head osteonecrosis. The rationale for using BP therapy for LCPD is the potential to prevent substantial femoral head deformity during the fragmentation phase by inhibiting osteoclastic bone resorption. Our purposes in this systematic review were to determine the effect of BP

therapy on the improvement of pain and function in LCPD and other juvenile osteonecrotic conditions and the prevention of femoral head collapse in clinical and experimental studies of femoral head osteonecrosis.

The limitations in the literature are numerous and primarily stem from the small number of published Level IV studies currently available for review. All studies were subject to selection bias. The patient populations represented a heterogeneous group with varying etiologies and stages of osteonecrosis. Only one study adhered to a standardized protocol for initiation and dosing of BP therapy, which is critical to understanding the effects of the drug on prevention of femoral head collapse and improving function. Furthermore, a clear radiographic classification of osteonecrosis pre- and posttreatment was not described in most studies, making it difficult to quantify the amount of deformity at the onset and conclusion of BP use. Objective radiographic data describing femoral head shape and correlative histologic information analyzing bone microarchitecture obtained from animal studies suggest BPs interfere with the biologic pathophysiology of femoral head collapse, but these findings remain to be confirmed in humans.

Fig. 4A–B (A) Radiographic findings from a study using a surgically induced osteonecrosis model in immature rats shows the animals receiving zoledronic acid either postoperatively (ZA Post) or preoperatively and postoperatively (ZA Pre-Post) had better preservation of the femoral head architecture compared to the animals receiving saline. The nonoperated femoral heads (Non-Op) from the animals receiving saline were used as normal controls. (B) Histologic sections (stain, von Kossa; original magnification $\times 25$) show increased bone resorption in the femoral head of a saline-treated animal compared to the femoral head of an animal treated with zoledronic acid postoperatively (ZA Post) or preoperatively and postoperatively (ZA Pre-Post). Reprinted with permission by The American Society of Bone and Mineral Research from Little DG, Peat RA, McEvoy A, Williams PR, Smith EJ, Baldock PA. Zoledronic acid treatment results in retention of femoral head structure after traumatic osteonecrosis in young Wistar rats. *J Bone Miner Res.* 2003;18:2016–2022.

Potential controversies regarding the use of BP therapy for the treatment of LCPD consist of limited distribution of the drug in necrotic bone, lack of bone anabolic effect, absence of a direct ability to enhance mechanical properties, and unknown long-term effects of therapy on the growing skeleton. It is important to recognize local bioavailability of BP for an avascular bone condition is impaired. A radioactive BP tracing study in the piglet model showed preferential binding of ^{14}C -ibandronate in the vascularized regions of the infracted femoral head [18] (Fig. 5). This finding explains why multiple dosing regimens are suggested for oral or intravenous administration. Local intraosseous administration has been investigated in the piglet model by injecting ^{14}C -ibandronate into the necrotic femoral heads and demonstrated a wide distribution of the drug with a reasonable retention over time [3] (Fig. 6). While a single local injection may effectively decrease the dose needed to exert the same desirable effect on decreasing femoral head deformity, this method also requires a secondary surgical procedure that introduces additional trauma to the ischemic bone.

The preservation of necrotic bone without new bone formation on the necrotic framework as observed in large-animal studies also raises the question of what effect BP therapy may have on bone formation in LCPD. An ideal biologic treatment for LCPD would restore the imbalance of bone resorption and formation that occurs during the fragmentation/resorptive phases. This prompted investigation of combined BP (antiresorptive) and BMP-2 (anabolic) therapy for femoral head osteonecrosis [45]. In comparison to controls, the combined therapy group had a decrease in femoral head asphericity and osteoclast number and an increase in trabecular bone volume and osteoblast surface, suggesting an additive effect of BMP-2 to increase bone formation. One cautionary finding from this study was the presence of heterotopic ossification in the hip joint capsule. Adjustment of the BMP-2 dose and refinement of the injection technique is paramount before applying this therapy in the clinical setting.

Several experimental studies suggest ischemic necrosis of the immature femoral head produces mechanical weakening of the cartilage and bone [20]. The likelihood of BP therapy to have an immediate effect on restoring the mechanical properties of the necrotic femoral head is small as this restoration depends on new bone formation that occurs over time. Since the healing process can be prolonged, especially in older patients with LCPD, a treatment regimen that combines protected weightbearing with a biologic agent to control bone resorption and formation may offer the best solution to avoiding mechanical compromise and ensuring long-term results.

In general, severe adverse effects due to BP therapy in children are uncommon when the drug is used judiciously

Fig. 5A–B (A) Autoradiographic images show the three regions (necrotic bone, revascularized marrow space, and newly formed bone) found in the infarcted femoral heads of piglets at 6 weeks after ischemia induction. ^{14}C -labeled ibandronate was administered intravenously 24 hours before sacrifice to determine its localization within the necrotic head. Arrows indicate the presence of silver grains (indicating ^{14}C radioactivity) on the trabecular surfaces. A dense concentration of the silver grains was present on the newly formed bone but not on the necrotic bone. (B) A bar graph shows the mean

silver grain counts obtained from the background and from the three regions found in the infarcted head at 6 weeks. ^a $p = 0.02$ versus background and $p = 0.05$ versus necrotic region; ^b $p = 0.000001$ versus all groups; HPF = high-power field. Reprinted with permission from Kim HK, Sanders M, Athavale S, Bian H, Bauss F. Local bioavailability and distribution of systemically (parenterally) administered ibandronate in the infarcted femoral head. *Bone*. 2006;39:205–212. Copyright Elsevier (2006).

[4, 13, 38, 40]. The most common side effect observed after intravenous administration is transient pyrexia with flulike symptoms; gastrointestinal effects were also reported. Osteonecrosis of the jaw has not been reported in the pediatric population. One of the unresolved questions pertains to the long-term effects of administering repetitive doses of BP on the normal growing skeleton. Since LCPD is a self-limiting disease, the duration of treatment arguably will be shorter than that for chronic conditions such as osteogenesis imperfecta. The drug may be required only in the initial and resorptive stages of the disease. While some data on the systemic skeletal effects of BP therapy in children with osteogenesis imperfecta have been reported in the literature [10, 37, 48], information on children with normal skeletons is scant. Decreased long-bone growth was

observed in several animal studies [7, 17, 25, 26] and postulated to be a dose-dependent effect where high-dose BPs were given to fast-growing animals. Such growth inhibition has not been seen in several clinical reports. Maintenance of height z-scores was found in a small cohort of children treated for fibrous dysplasia with pamidronate for 1.2 to 9.1 years [38] and another review of 17 patients with LCPD treated with zoledronic acid over an 18-month period [13].

In conclusion, experimental studies show a potential role for BPs to protect the femoral head from collapsing in conditions of osteonecrosis. Many questions remain to be clarified regarding the optimal dose of BP, timing of treatment initiation, and mode of drug delivery. Possible limitations of BP therapy include decreased distribution

Fig. 6A–B (A) A radiograph demonstrates an intraosseous needle placed in the central region of the femoral head used to locally deliver BP. (B) Autoradiographic sections from a control femoral head and an infarcted femoral head injected with ^{14}C -ibandronate show a wide distribution of ^{14}C -ibandronate, marked by diffuse staining of the trabecular bone with black silver grains, in the femoral head after a single intraosseous injection. (C) A representative radiograph and photomicrographs (stain, von Kossa and McNeal's tetrachrome; original magnifications, $\times 5$ and $\times 100$) obtained from an infarcted

femoral head injected with saline or 560 μg ibandronate 7 weeks before the sacrifice show femoral head structure and trabecular bone are better preserved in the ibandronate group than in the saline group. Reprinted with permission by The American Society of Bone and Mineral Research from Aya-ay JP, Athavale S, Morgan-Bagley S, Bain H, Bauss F, Kim HK. Retention, distribution and effects of intraosseously administered ibandronate in the infarcted femoral head. *J Bone Miner Res.* 2007;22:93–100.

within the necrotic bone after systemic administration, lack of a bone anabolic effect, and absence of an immediate enhancement of mechanical properties in the necrotic femoral head. Due to the lack of available clinical evidence, we cannot recommend the use of BP therapy in LCPD to prevent femoral head deformity and improve long-term functional outcome. Further basic science and clinical research are necessary to investigate the efficacy and safety of BP treatment in LCPD with a particular focus on the potential adverse events on remodeling of the necrotic bone and the rest of the growing skeleton. Any clinical trial must be appropriately powered and be well-defined in terms of age groups, stage of disease, and weightbearing status during the course of BP treatment. We are currently aware of one randomized clinical trial under

way in Australia comparing intravenous administration of zoledronic acid to a standard care (weightbearing restriction and current treatments) for LCPD (Clinical Trial Registration ACTRN12610000407099).

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