Clinical Review: Bisphosphonate Use in Childhood Osteoporosis

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Context: As awareness of osteoporosis in childhood has increased, so have pressures to consider use of the pharmacological agents used to treat osteoporosis in adults. This review examines available research on the efficacy and safety of bisphosphonate therapy for pediatric osteoporosis.

Evidence Acquisition: We reviewed the medical literature for key articles and consensus statements on the use of bisphosphonates in children through June 2008.

Evidence Synthesis: We compared reports using varying bisphosphonate agents, doses, and duration of therapy to treat osteogenesis imperfecta and a variety of secondary causes of osteoporosis in children. Conclusions drawn from a recently published Cochrane analysis and the consensus statements from experts in the field were considered as well.

Conclusions: Use of bisphosphonate therapy in pediatric patients remains controversial because of inadequate long-term efficacy and safety data. For this reason, many experts recommend limiting use of these agents to those children with recurrent extremity fractures, symptomatic vertebral collapse, and reduced bone mass. Current data are inadequate to support the use of bisphosphonates in children to treat reductions in bone mass/density alone. More research is needed to define appropriate indications for bisphosphonate therapy and the optimal agent, dose, and duration of use in pediatric patients. **(*J Clin Endocrinol Metab* 94: 400–409, 2009)**

Low bone mass and fragility fractures complicate several genetic and acquired disorders of childhood and adolescence (1–3). Forearm fractures in otherwise healthy youth also may reflect low bone mass, placing them at increased risk for future fractures (4–6). Attention to early skeletal fragility has increased with the use of bone densitometry and the improved long-term survival among children with malignancy, organ transplantation, cystic fibrosis, and other serious chronic illnesses. As awareness of bone fragility in childhood has grown, so have pressures to establish safe and effective therapies.

Despite a well-developed pharmacopoeia for treating osteoporosis in older adults, drug therapy for children remains a thorny issue. Bisphosphonates are the most widely prescribed drugs to treat osteoporosis in postmenopausal women, men, and adults on chronic systemic glucocorticoid therapy (7). In randomized controlled trials, these agents have proven effective in increasing bone mass and reducing fracture risk with acceptable safety profiles. Guidelines for bisphosphonate use in adults reflect extensive data on the favorable cost-benefit ratios (7–9).

Bone fragility in pediatric patients is sufficiently different to make it inappropriate to extrapolate from the literature in adults when treating children. Because compromised bone growth and mineral acquisition often contribute to osteoporosis in younger patients, an anabolic stimulus or drug would be optimal if a safe and effective method were available. Studies of the antiresorptive agents in children to date are inadequate to address all safety and efficacy concerns (1, 10). At present, experts recommend limited use of bisphosphonates in both primary (11) and secondary (12) osteoporosis in childhood. This review will outline the common disorders linked to osteoporosis in childhood, the pediatric safety and efficacy data for bisphosphonates in osteoporosis treatment, and the challenges to closing the gaps in current knowledge.

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Abbreviations: BMC, Bone mineral content; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; OI, osteogenesis imperfecta.

Diagnosis of Osteoporosis in Childhood

A panel of pediatric bone experts proposed that osteoporosis in younger patients be defined by "the presence of both a clinically significant fracture history and low bone mineral content or bone mineral density" (13). Low bone mass was defined as bone mineral content (BMC) or bone mineral density (BMD) Z-scores (for age, gender, and body size) below −2 SD; clinically significant fractures included one or more long bone fractures of the lower extremity, at least two long bone fractures of the upper extremity, or vertebral compression fractures. Lateral radiographs of the spine are valuable diagnostic studies because the trabecular bone at this site appears particularly sensitive to damage in chronic illness (14, 15). These diagnostic criteria were based upon expert opinion, leaving room for debate. For example, osteoporosis may be suspected in the presence of low trauma or vertebral compression fractures even if the BMD Z-score is better than −2 SD.

The emphasis on clinical bone fragility in diagnosing osteoporosis is appropriate given the challenges of interpreting densitometry in children. Pediatric BMD dual-energy x-ray absorptiometry (DXA) reports may be inappropriately interpreted using T-scores rather than age-adjusted Z-scores (16). Even when BMD is compared with appropriate age and gender reference data, the predictive value of low bone mass alone for future fracture risk in children remains uncertain (1). In otherwise healthy youth, fracture risk at the radius increased approximately 2-fold for every 1 SD that spine BMC or BMD fell below expected (4, 6). Adjusting bone mass and area for body size strengthened the correlation between densitometric data and fractures in cross-sectional (17) and prospective (18, 19) studies of healthy youth. Whether these adjustments will help to predict fractures in chronic illness remains to be determined.

Disorders Linked to Bone Fragility in Childhood and Adolescence

The myriad genetic and acquired disorders causing low bone mass and fractures in childhood (Table 1) have been previously reviewed (1–3). Osteogenesis imperfecta (OI), the most common of the inherited disorders, varies in severity from life-threatening skeletal weakness in the neonate to asymptomatic low bone mass in the adolescent (20). Similarly, the skeletal manifestations of chronic rheumatological, endocrine, immobilization, or gastrointestinal disorders vary considerably depending on age of onset, disease severity, and medication use. The causes of secondary osteoporosis in childhood are similar to those in adults, but the skeletal effects of these disorders in younger patients may differ. Bone growth in length and width may be compromised with or without concomitant loss of bone mineral (mass). Because the timing of epiphyseal fusion varies, the skeletal sites affected will vary with the developmental stage of the patient at onset of illness (21).

Fractures, particularly in the forearm region, occur in approximately one third of youth by age 17 (22, 23). When compared with youth who have not fractured, children with a fracture history have lower bone mass, reduced bone width, and an increased risk of subsequent fracture (4, 5, 24). Thus, recurrent fractures may be clinical indicators of unrecognized primary or secondary bone disorders such as OI, mutations in the low-density lipoprotein receptor-related protein 5 (LRP5) gene (25), or celiac or Crohn's disease.

A review of glucocorticoid-associated osteoporosis is illustrative of age-related differences in skeletal risk. In pharmacological doses, these agents contribute to increased bone resorption, impaired bone formation, reduced calcium absorption from the gut, urinary calcium loss, and diminished sex steroid and GH production (26). The end result is net bone loss in adults, whereas in growing children, both bone size and mass may be reduced as well (27). Osteoporosis in the context of glucocorticoid use is the most common form of secondary osteoporosis in older patients (26). The risk of fracture in older patients is sufficiently well established to justify the use of bisphosphonates as a primary prevention measure; bisphosphonate therapy is recommended for adults with low bone mass who will receive more than 3 months of systemic glucocorticoids (26).

Children who receive systemic glucocorticoids are also at increased risk for fracture. Based upon drug registry data, children prescribed more than three courses of systemic glucocorticoids yearly faced a 20% increase in age-adjusted fracture rates (28). Rapid recovery occurred once glucocorticoids were discontinued, and fracture rates returned to expected for age by 1 yr after treatment (28). Despite insights from this pediatric study, data on bone loss, fracture risk, and the potential for recovery from glucocorticoid effects remain too limited to support use of bisphosphonates as a primary prevention strategy in children (12).

Therapy: General Measures

Initial treatment for low bone mass and fractures in childhood is directed at reducing or eliminating modifiable skeletal risk factors (1–3). Daily intake of calcium and vitamin D through diet and supplements should meet recommended amounts for age (29). Based upon pediatric studies to date, an expert panel recommended maintaining serum 25-hydroxyvitamin D above 50 nmol/liter (20 ng/ml) in children (30); concentrations above 80 nmol/liter (32 ng/ml) are considered optimal in adults. Underweight or obesity should be addressed and immobilization or excessive activity avoided where possible. Endogenous or iatrogenic excess of thyroid or glucocorticoid hormones should be corrected. Sex steroid replacement is indicated for primary or secondary hypogonadism. Reducing the activity of the underlying disease causing osteoporosis is paramount to successful osteoporosis management. Although this may require increased doses of glucocorticoids, methotrexate, or other osteotoxic agents, the net benefit of reduced inflammation may outweigh adverse drug effects. Several inflammatory cytokines act through the receptor activator of nuclear factor-κB (RANK)/RANK ligand system to reduce bone formation and increase bone loss in a manner similar to glucocorticoids (31).

TABLE 1. Differential diagnosis of osteoporosis in children and adolescents (most common causes, based on current pediatric literature)

Category	Diagnosis
Primary osteoporosis	
Heritable disorders impacting bone and/or connective tissue development	OI
Idiopathic juvenile osteoporosis (including heterozygous mutations in *LRP5*)	Bruck syndrome
	Osteoporosis pseudoglioma syndrome
	Ehlers-Danlos syndrome
	Marfan syndrome
	Cutis laxa
Secondary osteoporosis	
Neuromuscular disorders	Cerebral palsy
	Duchenne muscular dystrophy
	Spinal cord injury
	Rett syndrome
	Prolonged immobilization for any reason
Chronic illness	Leukemia and other childhood cancers
	Rheumatologic disorders
	Anorexia nervosa
	Cystic fibrosis
	Inflammatory bowel disease
	HIV
	Renal failure
	Severe burns
	Other: thalassemia, celiac disease, organ transplantation
Endocrine and reproductive disorders	Hypogonadism
	Turner syndrome
	GH deficiency
	Hyperthyroidism
	Diabetes mellitus
	Hyperprolactinemia
	Athletic amenorrhea
	Glucocorticoid excess (Cushing's syndrome/disease)
Iatrogens	Glucocorticoids
	Methotrexate
	Cyclosporine
	Radiotherapy
	Medroxyprogesterone acetate
	GnRH agonists
	L-T_4 suppressive therapy
	Anticonvulsants
Inborn errors of metabolism	Lysinuric protein intolerance
	Glycogen storage disease
	Galactosemia
	Gaucher disease
	Homocystinuria

These general measures have proven effective. BMD increases with weight gain in patients with anorexia nervosa, even without the return of spontaneous menses (32, 33). By contrast, sex steroids have failed to improve BMD in randomized controlled trials to treat anorexia nervosa in young women (34, 35). For children with restricted mobility, gains in bone mass occur with even modest increases in skeletal loading through physical therapy (36) or standing on vibrating platforms (37). Regrettably these low-risk beneficial measures to improve bone health are often overlooked (38).

Treatment: Pharmacological Agents

Pharmacological therapy for osteoporosis may be considered for pediatric patients who fail to respond adequately to these general measures (1, 2, 10). PTH, the most effective anabolic agent for bone in adults, has a black box warning against its use in children and teens (39), because it has caused osteosarcoma in growing animals. Anticatabolic agents remain the only pharmacological alternative for younger patients at the present time (7).

Bisphosphonate treatment for children with OI became more widespread after iv pamidronate was shown to reduce bone pain and fractures in an open-label trial of 30 patients (40). Over the past two decades, a variety of oral and parenteral bisphosphonates have been used to treat OI as well as steroid-associated osteoporosis, cerebral palsy, muscular dystrophy, burns, idiopathic juvenile osteoporosis, and other pediatric disorders of bone fragility (2, 12).

A recent Cochrane review evaluated data on pediatric bisphosphonate use for secondary osteoporosis published up to

2007 (12). Of the 807 potentially relevant articles, only 33 were appropriate for analysis including six randomized controlled trials, two case-controlled trials, one cohort study, and 24 case studies or series. Because studies differed in the drugs and doses used, the disorders treated, and the clinical endpoints assessed, findings from the various randomized trials could not be combined for analysis.

Data from several pediatric trials using oral or parenteral bisphosphonates are summarized in Table 2 (41–55). BMD increased in response to oral alendronate in children after renal transplantation (49) and other illness requiring glucocorticoids (52, 56, 57). By contrast, gains in BMD with alendronate therapy in teens with anorexia nervosa were not significantly greater than those in patients receiving placebo after correcting for body weight (50).

Intravenous pamidronate therapy has been shown to increase BMD in children with cerebral palsy (48), extensive burns (51), steroid-treated nephropathy or rheumatological disease (53, 55), and chronic graft-*vs.*-host disease after hematopoietic cell transplantation (58). Intravenous neridronate improved height and BMD at the hip and spine in children with OI compared with controls (43).

Although gains in BMD observed with bisphosphonate therapy are encouraging, none of these studies was sufficiently powered to examine effects on vertebral or appendicular fractures. This distinction is important because changes in BMD may not reliably predict clinical endpoints. For example, treatment with daily oral alendronate (59) or intermittent iv neridronate (43) produced greater gains in BMD than placebo in children with OI. However, neither regimen was more effective than placebo in reducing bone pain and fractures. Similarly, there was no significant difference in quality of life for children with OI randomized to receive oral olpadronate compared with placebo (46).

The Cochrane review in children with chronic illness osteoporosis concluded that data are insufficient to support use of bisphosphonates as standard therapy (12). Short-term (3 yr) safety and efficacy data were sufficient, however, to justify their use on compassionate grounds in severe cases of clinical bone fragility (fractures and pain).

Choice of Bisphosphonates: Agent and Dose

There is no consensus regarding the optimal bisphosphonate agent in children, dosage, or duration of therapy. Table 3 provides a summary of some of the treatment protocols that have been used in pediatric patients (40–50, 52–56, 60–63). When comparing outcomes in these studies, it is important to underscore that differences in the ages and diagnoses of the subjects likely influence the skeletal response to drug therapy independent of the drug or dose employed. The dose of pamidronate used initially to treat OI (1 mg/kg · d for 3 d every 4 months) was extrapolated from treatment regimens for adults with Paget's disease (40). Other investigators have favored a single day infusion of 1 mg/kg every 3 months (60–62). The mean annualized gain in BMD treated with the higher-dose pamidronate regimen averaged 42% (40) as compared with 20% (60, 61) with the lower-dose regimens. However, the cohorts studied in the low-dose series included not only patients with OI but also children with steroid-associated osteoporosis, idiopathic juvenile osteoporosis, and other disorders for which the BMD response to bisphosphonates may be more modest. In children with cerebral palsy, annualized gains in BMD averaged 21–89% in the distal femur and 33% in the spine with the higher-dose pamidronate (48) *vs.* mean gains of 38% at the spine and 45% at the femoral neck with the lower dose (62). There are scant data comparing different bisphosphonate agents in the same clinical center. In one partially randomized, open-label trial in patients with OI, cyclical iv pamidronate (9 mg/kg · yr) and oral alendronate (1 mg/kg · d) appeared equally effective in increasing BMD (45). In studies using functional outcomes, both higher- and lower-dose pamidronate has resulted in reduced bone pain and fractures, even in patients with only modest changes in BMD (40, 60, 61). The lack of randomized trials comparing drugs and doses in various conditions makes it is impossible to declare one therapeutic regimen superior to another.

Duration of Therapy

Bisphosphonate therapy in adults has proven safe for 10 yr or more (64). Concerns about risks from oversuppression of bone turnover and avascular necrosis of the jaw, however, have led some to suggest a drug holiday after prolonged bisphosphonate use (65). The optimal duration of bisphosphonate therapy in young patients has not been established (11). Gains in BMC with bisphosphonates have been shown to plateau after 2–4 yr of therapy in children with OI (66). Transiliac histomorphometry has also shown that increases in cortical thickness and trabecular number are maximal after this duration of treatment (68).

Gains in bone mass achieved with bisphosphonates are sustained to varying extents after termination of drug therapy in children. Increases in spine and whole-body bone mass in burn patients treated with pamidronate persisted for up to 2 yr after treatment (69). Duration of gains in bone density after bisphosphonate therapy appears dependent, at least in part, upon the amount of residual bone growth. Teens with OI who were at or near final adult height maintained their spine bone mass for 2 yr after discontinuing pamidronate therapy (70). By contrast, bone mass declined in younger patients who were still growing when bisphosphonates were stopped. At the distal radial metaphysis, BMC Z-scores decreased by 2 or more SDs after termination of pamidronate, reflecting the addition of pamidronate-naive bone (70). By contrast, BMC Z-scores remained relatively stable at the metabolically less active diaphysis in these patients.

These findings underscore the potential risk of discontinuing bisphosphonate therapy in growing patients. In one study, fracture rates in children with OI during the first 2 yr after pamidronate were comparable to those during the previous 2 yr on therapy (71). However, others have observed long bone fractures at the junction of older, denser bone and new bone acquired after termination of pamidronate (70, 72). Therefore, concerns about

TABLE 2. Randomized or controlled clinical trials using bisphosphonate therapy in children with primary osteoporosis (OI) and osteoporosis due to chronic illnesses (neuromuscular disorders and systemic illness)

Author and year (Ref.)	Agent	No. of Participants	Mean age, yr (SD), unless otherwise specified	Diagnosis	Outcome	Results
Primary osteoporosis (OI)						
Randomized controlled trials						
Plotkin 2000 (41)	Pamidronate	15	Treatment, 10.6 months (6.8), historical controls 10.7 months (4.5)	OI	LS BMD, LS vertebral area, extremity fractures	BMD increased significantly in the treatment group and decreased in the control group ($P < 0.001$ for both); vertebral coronal area increased in all treated patients ($P < 0.001$) but decreased in the untreated group ($P < 0.05$); extremity fractures lower in the treatment group ($P < 0.05$)
Sakkers 2004 (42)	Oral olpadronate	34	Treatment 10.0 (3.1), control 10.7 (3.9)	OI	LS BMC, LS BMD	Significant difference in relative risk of fracture of long bones ($P = 0.01$), LS BMC ($P = 0.03$), LS BMD ($P = 0.01$)
Gatti 2005 (43)	iv neridronate	64	Treatment 9.0 (2.3), control 8.6 (2.4)	OI	LS BMD, hip BMD, no. of incident fractures	Significant difference in LS BMD and hip BMD ($P < 0.001$) and no. of incident fractures ($P < 0.05$)
Letocha 2005 (44)	iv pamidronate	18	Treatment 11.1 (2.4), control 10.0 (3.1)	OI	LS BMD, LS midvertebral height, total vertebral area	Significant difference in LS BMD ($P < 0.001$), LS midvertebral height ($P = 0.014$), and total vertebral area ($P = 0.003$) during the treatment phase but not during extended treatment
DiMeglio 2006 (45)	iv pamidronate *vs.* oral alendronate	18	8.7 (not reported)	OI	TB BMD, LS BMD	No significant differences in TB BMD or LS BMD between oral and iv therapy
Kok 2007 (46)	Oral olpadronate	34	Treatment 10.0 (3.1), control 10.7 (3.9)	OI	Pain, quality of life	No significant difference in pain score or quality of life
Controlled clinical trials						
Antoniazzi 2006 (47)	iv neridronate	25	0.09 (0.01)	OI	No. of incident fractures	Significant difference in no. of incident fractures ($P < 0.05$)
Osteoporosis secondary to neuromuscular disorders						
Randomized controlled trials						
Henderson 2002 (48)	iv pamidronate	12	Treatment 9.3 control 9.3	Nonambulatory, quadriplegic cerebral palsy	Distal femur BMD, LS aBMD	Significant difference in distal femur BMD raw score % change and Z-score ($P = 0.01$); LS aBMD raw score % change and Z-score not significant

(*Continued*)

TABLE 2. Continued

Author and year (Ref.)	Agent	No. of Participants	Mean age, yr (SD), unless otherwise specified	Diagnosis	Outcome	Results
Osteoporosis secondary to chronic systemic illness						
Randomized controlled trials						
El-Husseini 2004 (49)	Oral alendronate	30	Treatment 15.2 (3.5), control 14.6 (4.3)	Postrenal transplant	LS aBMD	Significant difference in LS BMD T-score ($P < 0.001$)
Golden 2005 (50)	Oral alendronate	32	Treatment 16.9 (1.6), control 16.9 (2.2)	Anorexia nervosa	L1-L4 aBMD, L1-L4 vBMD, L1-L4 BMC, femoral neck aBMD, femoral neck vBMD, femoral neck BMC	Significant difference in femoral neck vBMD % change ($P < 0.05$) but no significant difference in L1-L4 and femoral neck aBMD % change
Klein 2005 (51)	iv pamidronate	43	11.6 (3.8)	Burns on >40% total body surface area	LS BMC, TB BMC	Significant difference in LS BMC % change ($P < 0.005$) but no significant difference in TB BMC % change
Rudge 2005 (52)	Oral alendronate	22	Not reported for mean (SD); age range, 4.3–17.2 yr	Mixture of chronic illness	LS aBMD, LS vBMD, LS BMC, no. of incident fractures	No significant difference in LS aBMD Z-score ($P = 0.16$); within-group results: LS vBMD increased significantly in the alendronate group ($P = 0.013$) but not in the placebo group
Kim 2006 (53)	Oral pamidronate	44	Treatment 8.5 (4.49), control 8.5 (2.39)	Nephropathy	Mean LS aBMD	Between-groups comparisons not reported; within-group results: mean LS aBMD decreased in the control group ($P = 0.0017$) but not in the study group
Controlled clinical trials						
Lepore 1991 (54)	Oral disodium clodronate	13	Not reported	Active systemic or polyarticular juvenile chronic arthritis	T_{12}, L_1-L_3 BMD by CT	Between-groups comparisons not reported; within-group results: LS BMD by CT increased in the clodronate group, decreased in the control group (no statistical analyses reported)
Acott 2005 (55)	iv pamidronate	34	Not reported	Nephrology and rheumatology patients	L_1-L_4 aBMD, no. of incident fractures	Between-groups comparisons not reported; within-group results: aBMD Z-scores increased significantly relative to baseline (pamidronate *vs.* control) when measured at 6-monthly intervals until 30–36 months with repeated-measures ANOVA assessment ($F = 11.27$; $P = 0.0057$)

All results are presented as between-group analyses unless otherwise stated. aBMD, Areal BMD; CT, computed tomography; LS, Lumbar spine; TB, total body; vBMD, volumetric BMD.

TABLE 3. Bisphosphonate treatment protocols for pediatric disorders

Author and year (Ref.)	Drug	Dose[a]	Route	Illness
Glorieux 1998 (40)	Pamidronate	1 mg/kg · d for each of 3 d, every 4 months	iv	OI in children > age 3
Plotkin 2000 (41)	Pamidronate	0.5–1.0 mg/kg · d for each of 3 d, every 2 to 4 months	iv	OI in children ≤ age 2
Gandrud 2003 (60), Steelman 2003 (61), and Plotkin 2006 (62)	Pamidronate	1 mg/kg (max 30 mg) every 3 months	iv	OI > age 3, idiopathic juvenile osteoporosis, steroid-associated osteoporosis, Duchenne muscular dystrophy, HIV, spina bifida
Letocha 2005 (44)	Pamidronate	10 mg/m^2 · d for each of 3 d, every 3 months	iv	Children 4–16 yr of age with types III and IV OI
Henderson 2002 (48)	Pamidronate	1 mg/kg · d (not <15 mg or >30 mg) for each of 3 d, every 3 months	iv	Quadriplegic cerebral palsy
Acott 2005 (55)	Pamidronate	1 mg/kg (max 90 mg) every 2 months	iv	Nephrology and rheumatology patients
DiMeglio 2006 (45)	Alendronate, pamidronate	Alendronate, 1 mg/kg · d (max 20 mg/d); pamidronate, 1 mg/kg · d for each of 3 d, every 4 months	Oral, iv	OI in children > age 3
Antoniazzi 2006 (47)	Neridronate	2 mg/kg for 2 d every 3 months	iv	OI in the neonatal period
Gatti 2005 (43)	Neridronate	2 mg/kg every 3 months	iv	OI in prepubertal children
Hogler 2004 (63)	Zoledronate	0.25 mg/kg every 3 months	iv	Various bone disorders including osteoporosis and avascular necrosis
Sakkers 2004 (42) and Kok 2007 (46)	Olpadronate	10 mg/m^2 daily	Oral	OI with restricted ambulation (Sakkers) and children > age 3 (Kok)
Bianchi 2000 (56)	Alendronate	5 mg/d ≤20 kg; 10 mg/d >20 kg	Oral	Rheumatological disorders treated with glucocorticoids
El-Husseini 2004 (49)	Alendronate	5 mg/d	Oral	Postrenal transplantation
Golden 2005 (50)	Alendronate	10 mg/d	Oral	Anorexia nervosa
Rudge 2005 (52)	Alendronate	1–2 mg/kg · wk	Oral	Children with chronic illnesses treated with glucocorticoids
Lepore 1991 (54)	Clodronate	1200 mg daily in three divided doses	Oral	Active systemic or polyarticular juvenile chronic arthritis
Kim 2006 (53)	Pamidronate	125 mg/d	Oral	Nephropathy treated with glucocorticoids

[a] See original article for maximal dosing per kilogram per year.

the cumulative effect of bisphosphonate must be balanced against the risk for fracture with further growth. In younger patients with OI or persistent risk factors for compromised bone health, continued bisphosphonate therapy, perhaps in a lower dose, will likely be needed until growth is fully or nearly completed.

Adverse Effects of Bisphosphonates in Children

Bisphosphonates have generally been well tolerated in pediatric patients (10, 11, 40, 60). An acute-phase reaction including fever, malaise, nausea, diarrhea, and muscle or bone pain occurs in most children with the initiation of iv or oral agents. These symptoms begin typically within 1–3 d of initial exposure, last only a few days, and rarely recur with subsequent doses. Hypocalcemia, hypophosphatemia, and hypomagnesemia have been observed far less commonly, are typically asymptomatic, and resolve within days. To reduce the risk of these deficits, adequate vitamin D stores and calcium intake must be ensured before and throughout bisphosphonate treatment; using a lower initial dose of the more potent bisphosphonate, zoledronic acid, may also be helpful (73).

The more serious side effects linked to bisphosphonates in adults such as uveitis, thrombocytopenia, or esophageal or oral ulcerations are rare in children. Avascular necrosis of the jaw has not been reported with bisphosphonate therapy in any child or adolescent to date (74). Regardless, a dental evaluation is prudent before and during therapy in children with poor dental health. Other concerns may be unique to the younger patient. Severe respiratory distress has occurred with initiation of pamidronate therapy in infants with a prior history of reactive airway disease (75). In teen-aged girls, there is concern for potential adverse effects on reproductive health (76). The half-life of alendronate and pamidronate is estimated in years (77), and these agents can be released from bone years after termination of ther-

apy. Because these drugs readily cross the placenta, they may affect fetal development (78). High-dose bisphosphonate administration to pregnant rats has been linked to skeletal anomalies and hypocalcemia in the offspring (79). By contrast, only transient, asymptomatic hypocalcemia and an absence of skeletal anomalies attributable to the therapy have been reported in two infants delivered to mothers treated with bisphosphonates during or before pregnancy (80, 81). The full extent of reproductive risk remains uncertain because of small numbers of exposed fetuses. It is prudent to prescribe effective means of birth control to adolescent girls during bisphosphonate therapy and to consider performing a pregnancy test before each bisphosphonate infusion.

The adverse effect of greatest concern in the younger patient is oversuppression of bone modeling and remodeling with bisphosphonate use. Iatrogenic osteopetrosis and pathological fractures developed in a child treated for 2.75 yr with more than four times the high dose (9 mg/kg · yr) of pamidronate (82). Treatment with the standard high dose has not been shown to delay healing of spontaneous fractures but may delay healing of osteotomies in children with OI (83, 84). Some investigators have hypothesized that the oscillating saw and cautery used at surgery contribute to delayed healing in this setting (83).

The safe upper limit for each of the bisphosphonates in younger patients has not been established (11, 12). Children with OI treated with 9 mg/kg · yr of pamidronate have suppressed bone turnover markers compared with age-matched controls even 2 yr after discontinuing the drug (71). Reduction in bone modeling at the distal femur was observed with this dose in one study in OI patients (67) but not in another using lower doses of pamidronate to treat osteonecrosis (85). The clinical significance of these subtle morphological changes is not clear (67). Ultimately, comparing benefits and risks of higher compared with lower doses requires formal testing in randomized trials.

Bisphosphonate Research in Children

Key challenges to designing pediatric bisphosphonate trials include the selection of subjects and outcome measures. The risk to benefit ratio would be most favorable for children who have already sustained vertebral or long bone fractures. Limiting drug trials to patients with fractures, however, would narrow the pool of eligible subjects considerably. Whether bisphosphonate trials are justifiable in patients with documented longitudinal bone loss but no fractures can be debated. For these patients, it would be ideal to better define the natural history and potential for recovery before initiating pharmacological therapy. Such information could be gleaned by establishing registries for patients facing skeletal risk factors.

Designing a pediatric study sufficiently powered to examine fracture prevention is a Herculean task. Not only are fracture rates generally low in children, but fracture risk may also be reduced in the placebo group (treated with calcium and vitamin D for ethical reasons). Assuming enrollment of subjects with a fracture incidence of 7% annually, use of a highly efficacious drug (that reduced fractures by 60%), a 15% reduction of fractures in patients receiving placebo, and 15% attrition through a 3-yr study, a total of 406 subjects would be needed (Henderson, R. C., personal communication). Although this cohort size pales in comparison with the thousands in adult bisphosphonate trials, the barriers to pediatric drug studies are considerable. Funding from industry, government, and private agencies is less available, and resistance to pharmacological trials is far greater from parents, subjects, and investigational review boards.

Densitometric, biochemical, or functional indicators are attractive alternative outcome measures because changes can be noted in a shorter duration with fewer subjects (86, 87). Changes in BMD with therapy are imperfect predictors of future fracture, however, even in adults (86, 87). In pediatric patients, the influence of bone growth and secondary mineralization on BMD measurements must be factored in (89, 90). In addition, it is not certain how well changes in densitometric measures predict fracture risk for children with osteoporosis (12). Newer densitometry modalities such as peripheral and high-resolution peripheral quantitative computed tomography may ultimately prove valuable alternatives to DXA once challenges related to standardization of skeletal site and precision are resolved. Biochemical markers of bone metabolism must be adjusted for age and pubertal stages and may reflect the patient's muscle mass, growth pattern, and underlying disease rather than bone metabolism specifically (89, 90). As with bone density, changes in bone markers in response to drug therapy may not predict change in bone mass in pediatric subjects (12). Trans-ilial histomorphometry, although an invasive procedure, can be carried out safely in children and remains a valuable tool in the diagnosis and monitoring of bone disorders in children (68). Functional indices of improved skeletal health such as bone pain, vertebral morphometry, muscle (grip) strength, quality of life, mobility, and activity of daily living scales are readily quantifiable and have been employed (46, 59).

Safety concerns are best addressed not only in randomized, placebo-controlled trials but also with patient registries of bisphosphonate-treated children, similar to those that have been established to track events in GH-treated patients. Obtaining support for this costly but necessary observation will be challenging.

Conclusions

Myriad controversies surround the treatment of pediatric patients with osteoporosis. Identifying individuals at greatest risk for fracture is still problematic. The potential for recovery with general supportive measures and treatment of chronic disease alone remains uncertain (3). Despite these unknowns, clinicians may be pressured to prescribe bisphosphonate therapy by anxious colleagues or parents despite a lack of evidence to guide bisphosphonate use in children and teens. To establish the evidence-based recommendations for the optimal choice of agent, dose, and duration of treatment will require randomized, controlled pediatric trials. Until such data are available, conservative use of pharmacological agents for osteoporosis is recommended. Bisphosphonate therapy is considered part of routine clinical

care in many tertiary pediatric centers for children with moderate to severe OI. For osteoporosis associated with chronic illness, bisphosphonate treatment is recommended only in the setting of clinical trials or as compassionate therapy for children with reductions in bone mass/density associated with low-trauma extremity fractures and symptomatic vertebral compression (11, 12).

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References

1. **Bachrach LK** 2007 Consensus and controversy regarding osteoporosis in the pediatric population. Endocr Pract 13:513–520
2. **Ward L, Bachrach LK** 2008 Osteoporosis in childhood and adolescence. In: Marcus R, Feldman D, Nelson DA, Rosen CJ, eds. Osteoporosis. 3rd ed. Boston: Elsevier; 1095–1133
3. **Bianchi ML** 2007 Osteoporosis in children and adolescents. Bone 41:486–495
4. **Goulding A, Grant AM, Williams SM** 2005 Bone and body composition of children and adolescent with repeated forearm fractures. J Bone Miner Res 20:2090–2096
5. **Goulding A, Jones IE, Williams SM, Grant AM, Taylor RW, Manning PJ, Langley J** 2005 First fracture is associated with increased risk of new fractures during growth. J Pediatr 146:286–288
6. **Clark EM, Tobias JH, Ness AR** 2006 Association between bone density and fractures in children: a systematic review and meta-analysis. Pediatrics 117: e291–e297
7. **Miller PD** 2008 Bisphosphonates: pharmacology and use in the treatment of osteoporosis. In: Marcus R, Feldman D, Nelson DA, Rosen CJ, eds. Osteoporosis. 3rd ed. Boston: Elsevier; 1725–1742
8. **Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A; National Osteoporosis Guideline Group.** 2008 Case finding for the management of osteoporosis with FRAX®: assessment and intervention thresholds for the UK. Osteoporos Int 19:1395–1408
9. **Cummings SR, Ensrud K, Donaldson MG, Bauer DC, Sellmeyer D, Schousboe JT** 2008 The U.S. National Osteoporosis Foundation (NOF) guideline: recommendations for pharmacologic treatment. IBMS Bone KEy 5:137–141
10. **Batch JA, Couper JJ, Rodda C, Cowell CT, Zacharain M** 2003 Use of bisphosphonate therapy for osteoporosis in childhood and adolescence. J Paediatr Child Health 39:88–92
11. **Rauch F, Glorieux FH** 2005 Bisphosphonate treatment in osteogenesis imperfecta: which drug, for whom, for how long? Ann Med 37:295–302
12. **Ward L, Tricco AC, Phuong P, Cranney A, Barrowman N, Gaboury I, Rauch F, Tugwell P, Moher D** 2007 Bisphosphonate therapy for children and adolescents with secondary osteoporosis. Cochrane Database Syst Rev 2007: CD005324
13. **Bain S, Leonard MB, Bianchi M-L, Hans DB, Kalkwarf HJ, Langman CB, Rauch F** 2008 Official positions of the International Society for Clinical Densitometry and Executive Summary of the 2007 ISCD Pediatric Position Development Conference. J Clin Densitom 11:6–21
14. **Taskinen M, Saarinen-Pihkala UM, Hovi L, Vettenranta K, Makitie O** 2007 Bone health in children and adolescents after allogeneic stem cell transplantation: high prevalence of vertebral compression fractures. Cancer 110:442–451
15. **Sinigaglia R, Gigante C, Bisinella G, Varotto S, Zanesco L, Turra S** 2008 Musculoskeletal manifestations in pediatric acute leukemia. J Pediatr Orthop 28:20–28
16. **Gafni RI, Baron J** 2004 Overdiagnosis of osteoporosis in children due to misinterpretation of dual energy x-ray absorptiometry (DEXA). J Pediatr 144: 253–257
17. **Jones G, Ma D, Cameron F** 2006 Bone density interpretation and relevance in Caucasian children aged 9–17 years of age: insights from a population-based fracture study. J Clin Densitometry 9:202–220
18. **Clark EM, Ness AR, Bishop NJ, Tobias JH** 2006 Association between bone mass and fractures in children: a prospective cohort study. J Bone Miner Res 21:1489–1495
19. **Flynn J, Foley S, Jones G** 2007 Can BMD assessed by DXA at age 8 predict fracture risk in boys and girls during puberty? An eight-year prospective study. J Bone Miner Res 22:1463–1467
20. **Rauch F, Glorieux FH** 2004 Osteogenesis imperfecta. Lancet 363:1377–1385
21. **Seeman E** 1997 From density to structure: growing up and growing old on the surfaces of bone. J Bone Miner Res 12:509–521
22. **Cooper C, Dennison EM, Leufkens HG, Bishop N, van Staa TP** 2004 Epidemiology of childhood fractures in Britain: a study using the General Practice Research Database. J Bone Miner Res 19:1976–1981
23. **Bailey DA, Wedge JH, McCulloch RG, Martin AD, Bernhardson SC** 1988 Epidemiology of fractures of the distal end of the radius in children as associated with growth. J Bone Joint Surg 8:1226
24. **Ferrari SL, Chevalley T, Bonjour JP, Rizzoli R** 2006 Childhood fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility? J Bone Miner Res 21:501–507
25. **Hartikka H, Makitie O, Mannikko M, Doria AS, Daneman A, Cole WG, Ala-Kokko L, Sochett EB** 2005 Heterozygous mutations in the LDL receptor-related protein 5 (LRP5) gene are associated with primary osteoporosis in children. J Bone Miner Res 20:783–789
26. **Canalis E, Mazziotti G, Giustina A, Bilzekian JP** 2007 Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int 18:1319–1328
27. **Ward LM** 2005 Osteoporosis due to glucocorticoid use in children with chronic illness. Horm Res 64:209–221
28. **Van Staa TP, Cooper HG, Leufkens HG, Bishop N** 2003 Children and the risk of fractures caused by oral corticosteroids. J Bone Miner Res 18:913–918
29. **National Institutes of Health Consensus Conference** 1994 NIH consensus developmental panel on optimal calcium intake. JAMA 272:1942–1948
30. **Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M** 2008 Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 122:398–417
31. **Teitelbaum SL, Ross FP** 2003 Genetic regulation of osteoclast development and function. Nat Rev Genet 4:638–649
32. **Miller KK, Lee EE, Lawson EA, Misra M, Minihan H, Grinspoon K, Gleysteen S, Mickely D, Herzog D, Klibanski A** 2006 Determinants of skeletal loss and recovery in anorexia nervosa. J Clin Endocrinol Metab 91:2931–2937
33. **Misra M, Prabhakaran R, Miller KK, Goldstein MA, Mickley D, Clauss L, Lockhart P, Cord J, Herzog DB, Katzman DK, Klibanski A** 2008 Weight gain and restoration of menses as predictors of bone mineral density change in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab 93:1231–1237
34. **Klibanski A, Biller BM, Schoenfeld DA, Herzog DB, Saxe VC** 1995 The effect of estrogen administration on trabecular bone loss in young women with anorexia nervosa. J Clin Endocrinol Metab 80:898–904
35. **Grinspoon S, Thomas L, Miller K, Herzog D, Klibanski A** 2002 Effects of recombinant human IGF-I and oral contraceptive administration on bone density in anorexia nervosa. J Clin Endocrinol Metab 87:2883–2391
36. **Chad KE, McKay HA, Zello GA, Bailey DA, Faulkner RA, Snyder RE** 1999 The effect of a weight-bearing physical activity program on bone mineral content and estimated volumetric density in children with spastic cerebral palsy. J Pediatr 135:115–117
37. **Ward K, Alsop C, Caulton J, Rubin C, Adams J, Mughal Z** 2004 Low magnitude mechanical loading is osteogenic in children with disabling conditions. J Bone Miner Res 19:360–369
38. **von Scheven E, Gordon CM, Wypij D, Wertz M, Gallagher KT, Bachrach L** 2006 Variable deficits of bone mineral despite chronic glucocorticoid therapy in pediatric patients with inflammatory diseases: a Glaser Pediatric Research Network study. J Pediatr Endocrinol Metab 19:821–830
39. **Tashjian AH, Gagel RF** 2006 Teriparatide [Human PTH(1-34)]: 2.5 years of experience on the use and safety of the drug for the treatment of osteoporosis. J Bone Miner Res 21:354–365
40. **Glorieux FH, Bishop N, Plotkin H, Chabot G, Lanoue G, Travers RT** 1998 Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med 339:947–952
41. **Plotkin H, Rauch F, Bishop NJ, Montpetit K, Ruck-Gibis J, Travers R, Glorieux FH** 2000 Pamidronate treatment in children under 3 years of age. J Clin Endocrinol Metab 85:1846–1850
42. **Sakkers R, Kok D, Engelbert R, van Dongen A, Jansen M, Pruijs H, Verbout A, Schweitzer D, Uiterwaal C** 2004 Skeletal effects and functional outcome with olpandronate in children with osteogenesis imperfecta: a 2-year randomized placebo-controlled study. Lancet 363:1427–1431

43. **Gatti D, Antoniazzi F, Prizzi R, Braga V, Rossini M, Tato L, Viapiana O, Adami S** 2005 Intravenous neridronate in children with osteogenesis imperfecta: a randomized controlled trial. J Bone Miner Res 20:758–763
44. **Letocha AD, Cintas HL, Troendle JF, Reynolds JC, Cann CE, Chernoff EJ, Hill SC, Gerber LH, Marini JC** 2005 Controlled trial of pamidronate in children with types II and IV osteogenesis imperfecta confirms vertebral gains but not short-term functional improvement. J Bone Miner Res 20:977–986
45. **DiMeglio LA, Peacock M** 2006 Two-year clinical trial of oral alendronate versus intravenous pamidronate in children with osteogenesis imperfecta. J Bone Miner Res 21:132–140
46. **Kok DH, Sakkers RJ, Janse AJ, Pruijs HE, Verbout AJ, Castelein RM, Engelbert RH** 2007 Quality of life in children with osteogenesis imperfecta treated with oral bisphosphonates (Olpadronate): a 2-year randomized placebo-controlled trial. Eur J Pediatr 166:1155–1161
47. **Antoniazzi F, Zamboni G, Lauriola S, Donadi L, Adami S, Tato L** 2006 Early bisphosphonate treatment in infants with severe osteogenesis imperfecta. J Pediatr 149:174–179
48. **Henderson RC, Lark RK, Kecskemethy HH, Miller F, Harcke HT, Bachrach SJ** 2002 Bisphosphonates to treat osteopenia in children with quadriplegic cerebral palsy: a randomized, placebo-controlled trial. J Pediatr 141:644–651
49. **El Husseini AA, El-Agroudy AE, El-Sayed MF, Sobh MA, Ghoneim MA** 2004 Treatment of osteopenia and osteoporosis in renal transplant children and adolescents. Pediatr Transplant 8:357–361
50. **Golden NH, Iglesias EA, Jacobson MS, Carey D, Meyer W, Schebenddach J, Hertz S, Shenker IR** 2005 Alendronate for the treatment of osteopenia in anorexia nervosa: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 90:3179–3185
51. **Klein GL, Wimalawansa SJ, Kulkarni G, Sherrard DJ, Sanford AP, Herndon DB** 2005 The efficacy of acute administration of pamidronate on the conservation of bone mass following severe burn injury in children: a double-blind, randomized, controlled study. Osteoporos Int 16:631–635
52. **Rudge S, Hailwood S, Horne A, Lucas J, Wu F, Cundy T** 2005 Effects of once-weekly oral alendronate on bone in children on glucocorticoid treatment. Rheumatology (Oxford) 44:813–818
53. **Kim SD, Cho BS** 2006 Pamidronate therapy for preventing steroid-induced osteoporosis in children with nephropathy. Nephron Clin Pract 102:c81–c87
54. **Lepore L, Pennesi M, Barbi E, Pozzi R** 1991 Treatment and prevention of osteoporosis in juvenile chronic arthritis with disodium clodronate. Clin Exp Rheumatol 9(Suppl 6):33–35
55. **Acott PD, Wong JA, Lang BA, Crocker JF** 2005 Pamidronate treatment of pediatric fracture patients on chronic steroid therapy. Pediatr Nephrol 20: 368–373
56. **Bianchi S, ML, Cimaz R, Bardare M, Zulian F, Lepore L, Boncompagni A, Galbiati E, Corona F, Luisetto G, Giuntini D, Picco P, Brandi ML, Falcini F** 2000 Efficacy and safety of alendronate for the treatment of osteoporosis in diffuse connective tissue diseases in children: a prospective multicenter study. Arthritis Rheum 43:1960–1966
57. **Von Scheven E, Gordon C, Wypij D, Chagomeranan M, Shepherd J, Fan B, Wertz M, Bachrach L** 2007 Pediatric randomized placebo-controlled trial of alendronate for glucocorticoid-associated osteoporosis. Arthritis Rheum 56: L18 (Abstract)
58. **Carpenter PA, Hoffmeister P, Chesnut III CH, Storer B, Charubas PM, Woolfrey AE, Sanders JE** 2007 Bisphosphonate therapy for reduced bone mineral density in children with chronic graft-versus-host disease. Biol Blood Marrow Transplant 13:683–690
59. **Glorieux FH, Rauch F, Ward LM, et al** 2004 Alendronate in the treatment of pediatric osteogenesis imperfecta. J Bone Miner Res 19:S12 (Abstract)
60. **Gandrud LM, Cheung JC, Daniels MW, Bachrach LK** 2003 Low-dose intravenous pamidronate reduces fractures in childhood osteoporosis. J Pediatr Endocrinol 16:887–892
61. **Steelman J, Zeitler P** 2003 Treatment of symptomatic pediatric osteoporosis with cyclic single-day intravenous pamidronate infusions. J Pediatr 142:417–423
62. **Plotkin H, Coughlin S, Kreikemeier R, Heldt K, Bruzoni M, Lerner G** 2006 Low doses of pamidronate to treat osteopenia in children with severe cerebral palsy: a pilot study. Dev Med Child Neurol 48:709–712
63. **Hogler W, Yap F, Little D, Ambler G, McQuade M, Cowell CT** 2004 Short-term safety assessment in the use of intravenous zoledronic acid in children. J Pediatr 145:701–704
64. **Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA** 2004 Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 350:1189–1199
65. **Ott SM** 2005 Long-term safety of bisphosphonates. J Clin Endocrinol Metab 90:1897–1899
66. **Rauch F, Plotkin H, Zeitlin L, Glorieux FH** 2003 Bone mass, size, and density in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate therapy. J Bone Miner Res 18:610–614
67. **Land C, Rauch F, Glorieux FH** 2006 Cyclical intravenous pamidronate treatment affects metaphyseal modeling in growing patients with osteogenesis imperfecta. J Bone Miner Res 21:374–379
68. **Rauch F, Travers R, Glorieux FH** 2006 Pamidronate in children with osteogenesis imperfecta: histomorphic effects of long-term therapy. J Clin Endocrinol Metab 91:511–516
69. **Przkora R, Herndon DB, Sherrard DJ, Chinkes DL, Klein GL** 2007 Pamidronate preserves bone mass for at least 2 years following acute administration for pediatric burn injury. Bone 41:297–302
70. **Rauch F, Cornibert S, Cheung M, Glorieux FH** 2007 Long-bone changes after pamidronate discontinuation in children and adolescents with osteogenesis imperfecta. Bone 40:821–827
71. **Rauch F, Munns C, Land C, Glorieux FH** 2006 Pamidronate in children and adolescents with osteogenesis imperfecta: effect of treatment discontinuation. J Clin Endocrinol Metab 91:1268–1274
72. **Ward KA, Adams JE, Freemont TJ, Mughal MZ** 2007 Can bisphosphonate treatment be stopped in a growing child with skeletal fragility? Osteoporos Int 18:1137–1140
73. **Munns CF, Rajab MH, Hong J, Briody J, Hogler W, McQuade M, Little DG, Cowell CT** 2007 Acute phase response and mineral status following low dose intravenous zoledronic acid in children. Bone 41:366–370
74. **Rizzoli R, Burlet N, Cahall D, Delmas PD, Eriksen EF, Felsenberg D, Grbic J, Jontell M, Landesberg R, Laslop A, Wollenhaupt M, Papapoulos S, Sezer O, Sprafka M, Reginster JY** 2008 Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. Bone 42:841–847
75. **Munns CF, Rauch F, Mier RJ, Glorieux FH** 2004 Respiratory distress with pamidronate treatment in infants with severe osteogenesis imperfecta. Bone 35:231–234
76. **Marini JC** 2003 Do bisphosphonates make children's bones better or brittle? N Engl J Med 349:423–426
77. **Khan SA, Kanis JA, Vasikaran S, Kline WF, Matuszewski BK, McCloskey EV, Beneton MN, Gertz BJ, Sciberras DG, Holland SD, Orgee J, Coombes GM, Rogers SR, Porras AG** 1997 Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. J Bone Miner Res 12:1700–1707
78. **Papapoulos SE, Cremers CL** 2007 Prolonged bisphosphonate release after treatment in children. N Engl J Med 356:1075–1076
79. **Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A** 1999 Transplacental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. Teratology 60:68–73
80. **Munns CF, Rauch F, Ward L, Glorieux FH** 2004 Maternal and fetal outcome after long-term pamidronate treatment before conception: a report of two cases. J Bone Miner Res 19:1742–1745
81. **Andreadis C, Charalampidou M, Diamantopoulos N, Chouchos N, Mouratidou D** 2004 Combined chemotherapy and radiotherapy during conception and first two trimesters of gestation in a woman with metastatic breast cancer. Gynecol Oncol 95:252–255
82. **Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S** 2003 Bisphosphonate-induced osteopetrosis. N Eng J Med 349:457–463
83. **Munns CFJ, Rauch F, Zeitlin LZ, Fassier F, Glorieux FH** 2004 Delayed osteotomy but not fracture healing in pediatric osteogenesis imperfecta patients receiving pamidronate. J Bone Miner Res 19:1779–1786
84. **Pizones J, Plotkin H, Parra-Gracia JI, Alvarez P, Gutierrez P, Bueno A, Fernandez-Arroyo A** 2005 Bone healing in children with osteogenesis imperfecta treated with bisphosphonates. J Pediatr Orthop 25:332–335
85. **Ward K, Cowell CT, Little DG** 2005 Quantification of metaphyseal modeling in children treated with bisphosphonates. Bone 36:999–1002
86. **Bonnick SL, Shulman L** 2006 Monitoring osteoporosis therapy: bone mineral density, bone turnover markers, or both? Am J Med 119:25S–31S
87. **Reginster JY, Collette J, Neuprez A, Zegels B, Deroisy R, Bruyere O** 2008 Role of biochemical markers of bone turnover as prognostic indicator of successful osteoporosis therapy. Bone 42:832–836
88. **Seeman E** 2007 Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy? Bone 41:308–317
89. **Mora S, Pitukcheewanont P, Kaufman FR, Nelson JC, Gilsanz V** 1999 Biochemical markers of bone turnover and the volume and the density of bone in children at different stages of sexual development. J Bone Miner Res 14:1664–1671
90. **Rauchenzauner M, Scmid A, Heinz-Erifan P, Kapelari K, Falkensammer G, Griesmacher A et al** 2007 Sex-and age-specific reference curves for serum markers of bone turnover in healthy children from 2 months to 18 years. J Clin Endocrinol Metab 92:443–449