

Effects of bisphosphonates in children with osteogenesis imperfecta: an AACPDM systematic review

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LIST OF ABBREVIATIONS

AACPDM American Academy for Cerebral Palsy and Developmental Medicine
ICF International Classification of Functioning, Disability and Health
LOE Level of evidence
OI Osteogenesis imperfecta

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This systematic review of the effects of bisphosphonate treatment in children with osteogenesis imperfecta was conducted using the American Academy for Cerebral Palsy and Developmental Medicine methodology for developing systematic reviews of treatment interventions (Revision 1.1) 2004. Despite a large body of published literature, there have been only eight studies with a sufficiently high level of internal validity to be truly informative. These studies confirm improvement in bone density. Many, but not all studies, demonstrate reduction in fracture rate and enhanced growth. There has been extremely limited evaluation of broader treatment impacts such as deformity, need for orthopedic surgery, pain, functioning, or quality of life. Short-term side effects were minimal. Which medication and dosing regimen is optimal and how long patients should be treated are unclear. This body of evidence would be strengthened by a larger controlled trial, because many studies lacked adequate power to evaluate stated outcomes. These studies do not address the impacts of bisphosphonates in children with milder forms of osteogenesis imperfecta and severe forms that are not due to mutations in the type I pro-collagen gene (e.g. types VII and VIII). Additional research is needed into treatment of infants. More studies evaluating medication choices, optimal dosing, duration of treatment, post-treatment impacts, and long-term side effects are necessary.

The American Academy for Cerebral Palsy and Developmental Medicine (AAPDM) has undertaken the development of systematic reviews to summarize the literature about specific intervention strategies used to assist children with developmental disabilities. These reviews are not best-practice documents or practice guidelines, but rather they gather and present the best evidence for and against the effectiveness of an intervention. Their goal is to present the evidence about interventions in an organized fashion to identify gaps in evidence and help address new research that is needed. The Academy is neither endorsing nor disapproving of an intervention in these reviews. Every effort has been made to assure that AAPDM systematic reviews are free from real or perceived bias. Details of the disclosure and consensus process for AAPDM outcomes

reports can be viewed at <http://www.aacpdm.org>. Nevertheless, the data in an AAPDM systematic review can be interpreted differently, depending on people's perspectives. Please consider the conclusions presented carefully.

BISPHOSPHONATES IN OSTEogenesis IMPERFECTA

Osteogenesis imperfecta (OI) represents a heterogeneous group of conditions characterized by primary bone fragility. The incidence has been estimated at 1–2 per 20 000 births; however, milder forms of OI are probably under-recognized. In the majority of patients, OI results from a genetic mutation in the synthesis of type I collagen, resulting in deficiencies in collagen that can be quantitative (if no protein is produced) or qualitative (if an abnormal

protein is produced), or both.¹ These deficiencies form an abnormal collagen matrix, creating bone fragility.² In addition, the badly formed collagen matrix is more susceptible to the body's normal process of repair. The amount of bone is further reduced by osteoclastic removal of defective collagen rods. Osteoblasts have difficulty making the abnormal collagen and transferring it out of the cell. Despite maximal stimulation, the osteoblasts are unable to deliver proteins at an adequate rate, leading to a failure to synthesize an adequate amount of bone matrix, and osteoporosis results.

Traditionally, patients with OI were classified into four clinical subgroups using the Sillence criteria.³ As our understanding of the genotypic and phenotypic variability has advanced, the utility of this classification has been questioned. Some of the less common syndromes of bone fragility, which have been historically considered to be forms of OI, are not due to collagen defects. For example, type VI OI is due to a mineralization defect, and Bruck syndrome is due to an abnormality in bone specific telopeptidyl hydroxylase. Bone fragility syndromes (related to mutations in type I pro-collagen or mutations in genes encoding for proteins that modify type I pro-collagen, and some of unknown origin) are presented in Table SI (supporting information, published online).

Children with OI have clinical manifestations outside the skeletal system (e.g. hypoacusis, dentogenesis imperfecta, easy bruising, low muscle tone, weakness, central nervous system complications). However, this report is focused on the most prominent symptom, bone fragility.

No cure for OI is likely in the near future.⁴ The variety of mutations responsible for this condition and the difficulties in control of gene expression make the possibility of gene therapy distant. Bone marrow transplantation has been tried in research settings with limited success.⁵ Currently, treatment is focused on amelioration of symptoms. Orthopedic surgery is used to strengthen long bones by inserting telescopic rods, to minimize deformity resulting from fractures and to treat deformities such as kyphoscoliosis. Rehabilitation efforts include strengthening, maintaining range, optimizing body alignment, teaching compensatory strategies, and prescribing assistive equipment. Over the past 50 years, various potential medical treatments to improve bone fragility have been touted, come into vogue, and used to treat patients, only to be found unhelpful. These treatments have numbered more than 20, including eight hormones, six mineral compounds, three vitamins, and other miscellaneous treatments. In his 1981 review of the literature, Albright noted 'waves of interest ... with a flurry of activity focused on one medication for 20- to 30-year periods, followed in turn by a slow shift to the next agent.'⁶ He also noted that many of the proposed

treatments had published research reports in which the authors concluded a positive impact (e.g. 15 positive reports for calcitonin, 12 for estrogen, and 14 for vitamin D), but that no study had adequate controls. He cautioned against continued acceptance of potential treatments without adequate evaluation, including comparison with appropriate control populations.

In 1987 Devogelaer et al. first reported the use of a bisphosphonate to treat this condition.⁷ Its use was based on a hypothesis and extrapolated from bisphosphonate treatment in other bone conditions such as juvenile osteoporosis and Paget disease of bone. The structure of bisphosphonates is based on that of pyrophosphate, a naturally occurring substance known to inhibit bone metabolism. Bisphosphonates have evolved through time from the original compounds (e.g. etidronate) to second- and third-generation aminobisphosphonates such as pamidronate, alendronate, and risedronate. These compounds inhibit farnesyl-pyrophosphate synthase, a key enzyme in the 3-hydroxy-3-methylglutaryl-coenzyme-A reductase pathway required for isoprenylation of intracellular proteins.² This results in failure to attach lipids to proteins that are tethered to the cell membrane of osteoclasts, impairing their biological function and, in high concentrations, causing apoptosis. The bone resorption involved in remodeling is slowed. This results in a favoring of bone formation over resorption during remodeling.

METHOD OF REVIEW

This review was conducted using the AACPDMM methodology to developing systematic reviews of treatment interventions (revision 1.1) 2004.⁸

Inclusion criteria

This review is limited to studies in which the intervention was a bisphosphonate and the participants were children (aged <18y at time of treatment) with OI defined by the clinical features shown in Table SI. Studies that involved other populations were included if the data for children with OI were analyzed separately.

Literature search

The literature search included PubMed (from 1950 to April 2007), CINAHL (from 1982 to April 2007), and the Cochrane Database of Systematic Reviews for studies published in English. The search terms were (osteogenesis imperfecta AND [phosphonate OR bisphosphonate OR pamidronate OR alendronate OR risedronate OR clodronate OR etidronate OR olpadronate OR APD OR zoledronic acid OR neridronate]). Reference lists in studies and review articles and researchers knowledgeable about this intervention were also consulted to identify potentially

Table I: ICF Components of health

Dimension	Description
Body function/body structure (BF/BS)	Anatomical parts of the body (organs, limbs, and their components), and physiological and psychological functions of body parts and systems
Activity & participation (A&P)	Activity is the execution of a task or action by an individual Participation is involvement in a life situation
Environmental factors (EF)	Environmental factors make up the physical, social, and attitudinal environment in which people live and conduct their lives

Source: International Classification of Functioning, Disability and Health (ICF).⁹

relevant studies. Abstracts and, if needed, full text of articles were reviewed to exclude publications that were not reports of treatment. Of 109 citations, 70 met inclusion criteria.

Classification of the outcomes

Each study was assigned a level of evidence (LOE) ranging from I to V, according to the study design and methods used, and each outcome of LOE I–III studies was coded by a component of the International Classification of Functioning, Disability and Health (ICF;⁹ Table I). LOE classifications are based on a hierarchy of research designs that range from the greatest to least according to ability of the design alone to reduce bias.¹⁰ Table II shows the hierarchy by research design used for AACPDM reviews. Even if a study is rated high in terms of LOE, it may still have

methodological limitations that could influence the results of the study. Studies rated LOE I–III^{11–18} were further assessed for the presence or absence of these specific design characteristics. Using the total score from this evaluation, each study was assigned a conduct rating of strong, moderate, or weak. This assessment is based on a series of questions provided in Table III. The conduct ratings of the higher-level studies (LOE I–III)^{11–18} are provided in Table III so that the reader can determine the strengths and weaknesses of each study. The findings for each outcome of interest in all of the LOE I–III studies are provided in Table IV categorized by component of health.^{11–18} Table V summarizes reported short- and long-term complications of bisphosphonate treatment.^{19–54} A complete list of all relevant studies considered in this systematic review is provided in Table SII (supporting information published online).^{7,11–28,32,33,35–45,47–80}

Table II: American Academy for Cerebral Palsy and Developmental Medicine levels of evidence: hierarchy of research designs

Level	Intervention (group) studies
I	Systematic review of randomized controlled trials (RCTs) Large RCT with narrow confidence intervals ($n > 100$)
II	Smaller RCT with wider confidence intervals ($n < 100$) Systematic review of cohort studies Outcomes research (very large ecological studies)
III	Cohort study (must have concurrent control group) Systematic review of case–control studies
IV	Case series Cohort study without concurrent control group (i.e. with historical control group) Case–control study
V	Expert opinion Case study or report Bench research Expert opinion based on theory or physiological research Common sense/anecdote

Source: Centre for Evidence-Based Medicine.¹⁰

ANALYSIS AND DISCUSSION OF THE EVIDENCE

1. What evidence exists about the effects of the bisphosphonate intervention in the component of ICF in which it was expected to work, (body function and body structure)?

Seven outcomes about body function and structure are available from studies with LOE I–III.^{11–16} Changes in bone metabolism markers were not consistent across studies. Increased bone density was documented in the spine, femoral neck, hip (all measured by dual-energy X-ray absorptiometry, DEXA), and tibia (measured by peripheral quantitative computed tomography). These DEXA changes were replicated in many studies. No changes were seen in bone density in the calcaneus measured by ultrasound; however, the validity of this methodology in pediatrics has not been determined. Observed impacts on linear growth were conflicting, with statistically significant positive effects on growth documented in two of five studies. Vertebral shape improvements reached statistical significance in one study. A reduction in non-vertebral fracture rate was demonstrated in several studies and was statistically

Table III: Quality of study conduct (studies with evidence levels I–III only)

Study	Level	Quality ^a	Question ^b						
			1	2	3	4	5	6	7
Sackers et al. ¹¹	II	Strong	Y	Y	Y	Y	N	Y	Y
Gatti et al. ¹²	II	Moderate	Y	Y	Y	N	N	Y	Y
Letocha et al. ¹³	II	Moderate	Y	Y	Y	N	N	Y	Y
Seikaly et al. ¹⁴	II	Moderate	Y	Y	Y	Y	N	Y	N ^c
Antoniazzi et al. ¹⁵	II	Moderate	Y	N	Y	N	N	Y	Y
Rauch et al. ¹⁶	III	Moderate	Y	Y	Y	N	N	Y	Y
DiMeglio et al. ^{17,18}	II	Weak	N	N	Y	N	N	Y	Y

^aThe quality of the study conduct is judged as strong if 6 to 7 questions are answered 'yes', moderate if 4 to 5 questions are answered 'yes', and weak if ≤3 questions are answered 'yes'.

^bQuestions were as follows:

1. Were inclusion and exclusion criteria of the study population well described and followed?
2. Was the intervention well described and was there adherence to the intervention assignment? (For 2-group designs, was the control exposure also well described?)
3. Were the measures used clearly described, valid, and reliable for measuring the outcomes of interest?
4. Was the outcome assessor unaware of the intervention status of the participants (i.e. was there blind assessment)?
5. Did the authors conduct and report appropriate statistical evaluation, including power calculations?
6. Were dropouts or losses to follow-up reported, and were they less than 20%? For 2-group designs, was dropout balanced?
7. Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?

^cAlendronate has treatment effects for some time after discontinuation, so half of the control group may have had treatment effects during their observation period.

significant in three studies. The reduction in fracture rate was clinically significant, ranging from 30 to 60%. There was no significant difference between the treatment and control groups on measures of muscle strength. Reductions in pain and analgesic use were documented by Seikaly et al.¹⁴ but not replicated by Letocha et al.¹³

2. What evidence exists about the effects of bisphosphonate intervention in the other components of ICF?

Activity and participation

Positive impacts on self-care and well-being were documented by Seikaly et al.¹⁴ However, other studies did not replicate these findings. Several studies evaluated impacts on mobility, ambulation, and functional status and found no statistically significant change.

Environmental factors

One study looked at the need for caregiver assistance and found no impact.¹¹

3. What evidence exists for linkages within and across these components?

Several studies support linkages between changes in bone metabolism, bone density or mineral content, and reduced

fracture risk.¹¹ One study supports a linkage between bone density improvements, pain reduction, enhanced self care, and well-being.¹⁴

4. What kinds and magnitude of medical complications have been documented?

The many published cohort studies as well as the more recent randomized trials allow monitoring of side effects in a substantial number of patients. It is reassuring that very few serious short-term side effects have been observed. Those seen were generally mild and reversible. The most common short-term side effects were fever and body aches reported with first infusion. Hypocalcemia was reported in numerous studies, but serious complications were reported in only one study. This was a neonate who experienced seizures due to hypocalcemia.³¹ Deterioration in respiratory function with need for intensive care support has been observed in several infants with pre-existing respiratory compromise.³⁹ Several authors raised concern regarding the difficulties with intravenous access and the impact that recurrent hospitalization might have in the functioning, activity, and environmental-context components of health. In one retrospective study, pamidronate treatment was associated with delayed healing of osteotomy sites after intramedullary rodding procedures.⁴⁰ A prospective cohort

Table IV: Summary of studies: outcomes, measures, and results

Outcome of interest	Measure	Component of health	Result
<i>A. Studies with evidence levels I–III</i>			
<i>Sakkers et al.¹¹ (level II–strong)</i>			
Bone density	DEXA, spine z-score	BF/BS	Increased in both groups but more so in treated patients ($p=0.002$)
Bone density	Calcaneal bone mineral content and density	BF/BS	No significant difference between groups
Vertebral shape	Lumbar vertebral height on plain radiograph	BF/BS	No significant difference between groups
Fracture risk	Radiographically confirmed non-vertebral fractures	BF/BS	31% risk reduction in treated group vs placebo ($p=0.01$)
Muscle strength	Hand-held myometer, shoulder abduction, grip, hip flexion	BF/BS	No significant difference between groups
Growth	Body/seated height, arm span, head circumference, weight	BF/BS	No significant difference between groups
Bone metabolism	Urinary C-telopeptides, deoxypyridinolines	BF/BS	No significant difference between groups
Self-care and mobility	PEDI	A&P	No significant difference between groups
Ambulation	Bleck scale	A&P	No significant difference between groups
Caregiver assistance	PEDI	EF	No significant difference between groups
<i>Gatti et al.¹² (level II–moderate)</i>			
Bone density	DEXA, spine, femoral neck & hip	BF/BS	Both groups improved, but pamidronate group improved more reaching significance ($p<0.05$) for lumbar spine at 6 months, and spine, femoral neck, & hip at 12 months
Vertebral shape	DEXA, projected area of lumbar vertebrae	BF/BS	Both groups improved, but pamidronate group improved more ($p<0.05$)
Bone metabolism	Alkaline phosphatase (total/bone)	BF/BS	Decreased in both groups. No statistical comparison provided
Fracture rate	Clinical report of fracture, non-vertebral	BF/BS	Lower relative risk of any fracture during follow up with pamidronate group (0.6, 95% confidence interval 0.21–1.59)
Growth	Height	BF/BS	Increased in both groups, but more substantial in treated group ($p<0.05$)
<i>Letocha et al.¹³ (level II–moderate)</i>			
Bone density	Lumbar spine DEXA z-score	BF/BS	Increased in treated group ($p<0.001$) and unchanged in control (intergroup $p<0.001$)
Bone density	Peripheral quantitative computed tomography z-score	BF/BS	Increases in treatment group (not significant vs baseline but $p<0.05$ vs control group, who had an average decline in z-score)
Vertebral shape	Summed L1–L4 midvertebral height, vertebral area	BF/BS	Treated patients had ‘significantly greater rate of increase than controls’ (p value not reported)
Fracture rate	Time to first fracture	BF/BS	Longer in treated group but not significantly different from control group ($p=0.6$)
Fracture rate	Change in rate of fractures vs baseline	BF/BS	No intergroup comparison
Gross motor function	Brief Assessment of Motor Function scale	A&P	Unchanged
Muscle strength	Lower-extremity and abdominal manual muscle strength testing	BF/BS	Unchanged
Pain	National Institutes of Health Functional Assessment pain score	BF/BS	Unchanged
Growth	cm/y	BF/BS	Unchanged
Bone metabolism	Bone-specific alkaline phosphatase, osteocalcin, procollagen peptide type I	BF/BS	Unchanged

Table IV: Continued

Outcome of interest	Measure	Component of health	Result
<i>Seikaly et al.¹⁴ (level II–moderate)</i>			
Bone density	Vertebral DEXA	BF/BS	Improved in treatment phase ($p < 0.01$)
Mobility	PEDI	A&P	Improved in treatment and placebo phases (difference not significant)
Self-care	WeeFIM	A&P	More improvement in treatment phase ($p < 0.01$)
Well-being	Not specified	A&P	Improved in both phases but more so during treatment ($p < 0.0001$)
Pain	Not specified	BF/BS	Reduced during treatment phase and increased during placebo phase ($p < 0.001$)
Pain	Days per week of analgesic use	BF/BS	Reduced analgesic use during treatment phase and increased use during placebo phase ($p < 0.05$)
Growth/nutrition	Body mass index	BF/BS	Unchanged
Bone metabolism	uNTX	BF/BS	Reduced during treatment and placebo phases but more so during treatment ($p < 0.01$)
Bone metabolism	Calcium, osteocalcin, PTH, dihydroxy vitamin D, urinary hydroxyproline	BF/BS	Unchanged
<i>Antoniazzi et al.¹⁵ (level II–moderate)</i>			
Bone metabolism	Serum calcium, phosphate, 25-hydroxy vitamin D, osteocalcin, uCa/uCr, uNTX/uCr	BF/BS	Unchanged except uCa/uCr, uNTX/uCr declined but not significantly vs control
Growth/nutrition	Insulin-like growth factor 1	BF/BS	Increased but not significantly vs control
Growth/nutrition	Recumbent length z-score	BF/BS	Improved ($p < 0.05$)
Growth/nutrition	Weight z-score	BF/BS	Improved ($p < 0.05$)
Fracture rate	Clinically identified and radiologically confirmed fractures (excluded vertebral fractures and those identified at delivery)	BF/BS	Reduced ($p < 0.05$, 2.4 vs 6.0 fractures/year)
Bone formation	Projected lumbar vertebral area	BF/BS	Improved but not significantly vs control
Bone pain	Parent report, method not specified	BF/BS	Reduced but no statistical analysis
<i>B. Studies evaluating discontinuation of bisphosphonates</i>			
<i>Rauch et al.¹⁶ (level III–moderate)</i>			
Bone metabolism	Serum alkaline phosphatase, PTH, calcium, vitamin D, phosphorus; uCa, uNTX	BF/BS	Most changes not significant, except for NTX/creatinine which increased off pamidronate ($p < 0.02$)
Bone mineral content	Lumbar spine DEXA	BF/BS	Decreased with treatment discontinuation, increased with treatment continuation ($p = 0.04$)
Fracture rate	Absolute number of clinical fractures	BF/BS	More fractures in discontinuation group (not significant)
Functional status	PEDI	A&P	No change
Mobility status	PEDI	A&P	No change
Growth	Weight z-score	BF/BS	Gained slightly off pamidronate (not significant vs control)
Growth	Height z-score	BF/BS	Declined slightly off pamidronate (not significant vs control)
<i>C. Studies comparing different bisphosphonates</i>			
<i>DiMeglio et al.¹⁷ (level II–weak)</i>			
Bone density	Total body and lumbar DEXA	BF/BS	No difference between groups

Table IV: Continued

Outcome of interest	Measure	Component of health	Result
Linear growth	Height	BF/BS	No difference between groups
Bone metabolism	Alkaline phosphatase (total & bone), uNTX, osteocalcin, intact PTH, vitamin D	BF/BS	No difference between groups
Fracture incidence	Radiographically confirmed fractures	BF/BS	No difference between groups
<i>DiMeglio and Peacock¹⁸ (oral alendronate vs intravenous pamidronate)</i>			
Bone mineral density	Body and lumbar spine bone mineral density	BF/BS	Increased similarly in both groups
Bone turnover		BF/BS	Decreased similarly in both groups
Fracture incidence		BF/BS	Decreased similarly in both groups (not significant)
Growth		BF/BS	Increased similarly in both groups

A&P, activity and participation; BF/BS, body function/body structure; DEXA, dual-energy X-ray absorptiometry; EF, environmental factors; PEDI, Pediatric Evaluation of Disability Inventory; PTH, parathyroid hormone; uCa, urinary calcium; uCR, urinary creatinine; uNTX, urinary N terminal telopeptides of type I collagen; WeeFim, functional independence measure for children.

study monitored closely and found no increase in delayed healing compared with historical observations in patients with OI. However, with only eight patients (24 bones surgeries, mean 1.6 [SD 0.84] osteotomies per bone), the study may not be adequately powered to exclude delayed healing as a complication.⁴⁵ Other short-term side effects are listed in Table V. While osteopetrosis has been reported in one child treated with bisphosphonates, it was not observed in any study in which bisphosphonates were used for treatment of OI or in any population using similar dosing regimens.^{45,81} The total numbers of patients across studies is not adequate to evaluate very rare but serious side effects such as esophagitis due to alendronate or osteonecrosis.

A small number of children were treated for up to 5 years and a few to 8 years with no reported long-term side effects. One author suggested caution regarding the potential impact of decreased bone remodeling and increased calcified cartilage over the long term.^{30,81} Urinary excretion of pamidronate has been documented up to 8 years after cessation of treatment, and concerns have been raised regarding the potential for this to affect fetal development in previously treated pregnant women.^{30,82} One retrospective review looked at outcomes in 24 women treated before pregnancy or in early pregnancy with alendronate and noted no major teratogenesis.⁸³ Biochemical analysis and follow-up of the infants was limited. Munns et al. reported on two infants born to women with OI who received pamidronate before conception,⁸⁴ and Cabar et al. reported on one infant.⁸⁵ The mothers suffered no ill effects. In the study by Munns et al.,⁸⁴ both infants had inherited OI. Neither infant had skeletal modeling abnormalities. One infant had transient asymptomatic

hypocalcemia at 24 hours of age (biochemical assessment was not available on the other infant at that age), and one infant had bilateral talipes equinovarus.

5. What is the strength of the evidence?

A large body of research exists relevant to potential impacts of bisphosphonates in OI. The vast majority of this research was completed with study designs that have limited internal validity. These studies have the potential to be misleading, particularly if a systematic uncontrolled variable is affecting results across all studies. Possible systematic confounders include the lack of blinding, lower fracture rates with advancing age, impacts of change in care due to study participation or time, and treatment effects of vitamin D and calcium supplementation. While studies with low levels of internal validity support the potential for a treatment to have a measured impact, research with stronger internal validity is required to confirm these effects.

In the past 3 years, studies that have stronger internal validity have been published with a consistent finding of improved bone density. Reduction of fracture risk has been demonstrated in three of four small, randomized controlled trials and appears to be in the range of 30 to 60%. The extent to which this reduction in fracture risk is clinically important may depend on a particular child's underlying fracture rate, the severity of the fractures, the pain associated with the fractures, and the invasiveness of procedures needed to manage those fractures. In these studies, potential confounders remain, as the published reports did not describe possible differences between the treatment and control groups with regard to intramedullary rods or external bracing at the time of recruitment or during the

Table V: Medical complications and adverse effects of bisphosphonates

Study	Effect	Cases
Bishop et al. ¹⁹	Fever	6
Bembi et al. ²⁰	Transient hyperthermia	3
Fujiwara et al. ²¹	Transient high fever and slight lowering of serum calcium	
Shaw ²²	Difficulty with intravenous access	1
Astrom and Soderhall ²³	Transient hypocalcemia	3
	Restriction in social life of child/family due to monthly hospitalization	3
Glorieux et al. ²⁴	Acute-phase reaction to first infusion	26
	Minimal decrease in serum calcium (asymptotic)	NR
	Back and limb pain	NR
Kodama et al. ²⁵	Increase in fracture rate when growth hormone was added to treatment	1
Plotkin et al. ²⁶	Acute-phase reaction with first infusion	9
	Mild decrease in serum calcium	7
Gonzalez et al. ²⁷	Hyperthermia, nausea, vomiting, dizziness, mild abdominal pain with first dose	
Lee et al. ²⁸	Transient low-grade fever with first infusion	
Banerjee et al. ²⁹	Low serum calcium (3 patients treated with 'calcium and vitamin D supplements')	6
Rauch et al. ³⁰	Decreased bone remodeling rate 'not necessarily beneficial in the long-term, as microdamage might accumulate in the bone tissue'	100%
	Increased calcified cartilage	NR
	No clinical consequences observed in study but authors felt these should be monitored when treating patients because of potential for harm	
Chien et al. ³¹	Hypocalcemia with seizure	1
Falk et al. ³²	Hypocalcemia without clinical symptoms during 2 of 57 treatment cycles	2
	Flu-like syndrome on first infusion	5
	IV infiltration	2
	Metallic taste	1
	Transient tachycardia	1
	Non-union at recurrent fracture site	1
Grissom and Harcke ³³	Transient pyrexia, nausea, joint pain	NR
Rauch et al. ³⁴	Short term: ionized calcium decreased in study group as a whole vs baseline (not requiring treatment, positive Chvostek's sign in some, no other symptoms); drop in calcium level largest at first infusion vs later treatment intervals; elevated parathyroid hormone with first infusion	Whole group
	Long term: no change in serum calcium, serum phosphorus decreased with time initially, then stable; parathyroid hormone levels elevated in 7	7
Adiyaman et al. ³⁵	Elevated blood urea nitrogen without change in renal function or ultrasound	1 of 8
Arikoski et al. ³⁶	Flu-like reaction with fever and muscle aches, typically with first course	Majority
Bin-Abbas et al. ³⁷	Sclerotic metaphyseal bands	10 of 10
DiMeglio et al. ³⁸	Fever	NR
Munns et al. ³⁹	Worsening respiratory status in infants with pre-existing respiratory compromise	4
Munns et al. ⁴⁰	Delayed healing of osteotomies (relative risk 7.29, 95% confidence intervals 2.62–20.3)	
Zacharin and Kanumakala ⁴¹	Fever	NR
Cho et al. ⁴²	Intermittent abdominal discomfort with alendronate; only one patient needed to discontinue treatment	6 of 16
DiMeglio et al. ¹⁷	Fever, myalgias, vomiting	NR
Forin et al. ⁴³	Fever with first infusion	19 of 29
	Fever with subsequent infusion	5 of 29
	Hypocalcemia with tremor treated with intravenous calcium in an infant	1

Table V: Continued

Study	Effect	Cases
Gatti et al. ¹²	Flu-like illness first infusion	10 of 42
Munns et al. ⁴⁴	Decreased bone formation rate per bone surface 17% that of historical controls	
	Mineralized growth plate material in secondary bone	
Pizonas et al. ⁴⁵	Case series showed one case of non-union (causing no functional problems) in seven children with a total of 20 fractures and 24 surgeries involving osteotomy	1 of 7
Seikaly et al. ¹⁴	Mild gastrointestinal intolerance with daily alendronate	2 of 17
Ward et al. ⁴⁶	Single dose of alendronate resulted in:	
	Headache	7 of 24
	Nausea	7 of 24
	Fever	5 of 24
	Abdominal pain	6 of 24
	Symptoms more prominent with oral than intravenous administration	
Antoniazzi et al. ¹⁵	Febrile reaction after first infusion; despite young age at first infusion, all infants tolerated the infusion well	9 of 10
DiMeglio and Peacock ¹⁸	Fever, myalgia, vomiting in pamidronate group only	NR
El Sobky et al. ⁴⁷	Fever, vomiting, transient bony aches, surgical complications similar in both groups	NR
Goksen et al. ⁴⁸	Pyrexia and hypocalcemia after first infusion.	3
Land et al. ⁴⁹	Interference with periosteal resorption of unclear clinical significance	
Vallo et al. ⁵⁰	Decreased plasma calcium and inorganic phosphate in first 3 treatment days (not requiring treatment)	NR
	Flu-like symptoms with first cycle	6 of 10
Zeitlin et al. ⁵¹	Acute-phase reaction after first infusion	Majority
	Mild hypocalcemia after first infusion	
Astrom et al. ⁵²	Fever after first infusion	5
Choi et al. ⁵³	Fever after first infusion	4
Land et al. ⁵⁴	Fever and skeletal pain after first infusion	Majority
	Transient asymptomatic hypocalcemia, increased parathyroid hormone, decreased serum phosphorus, and increased 25-hydroxy vitamin D	NR

NR, not reported.

study. Additionally, the studies did not include vertebral fractures in their calculation of fracture rate.

Positive impacts on growth, vertebral area, self-care, well-being, and pain were seen in small numbers of patients, but not all studies evaluating these impacts demonstrated improvements. No study reported power calculations, and these small studies likely lacked adequate power to exclude the potential for these positive impacts.

This body of evidence is exceedingly limited in the number of children evaluated in studies with LOE I–III. These research results are based on a total of only 101 treated individuals. The data for treatment of infants are extremely limited, with only five treated infants compared with five untreated infants in a randomized prospective fashion. This body of evidence is neither robust nor comprehensive enough to allow confident generalization to groups of

people at large. Furthermore, because studies have been focused on children with more severe disease, this body of research is not informative about the role of bisphosphonates in children with mild type I OI or other forms of OI that are not related to collagen mutations.

SUMMARY AND DIRECTIONS FOR FUTURE RESEARCH

Reduction of bone fracture rate, decrease in pain, and improvements in function and societal participation are the stated goals in bisphosphonate treatment of children who have OI. There have been eight studies with a sufficiently high level of internal validity to be truly informative. These studies confirm improvement in bone density. Many, but not all studies, demonstrate reduction in fracture rate and enhanced growth. Bisphosphonates do not eliminate

fracture risk, and they are not a cure for this disease. There has been extremely limited evaluation of broader treatment impacts, such as deformity, need for orthopedic surgery, pain, functioning, or quality of life. Which medication and dosing regimen is optimal and how long patients should be treated are unclear. One study attempted to compare treatment efficacy of different bisphosphonates (i.e. pamidronate and alendronate). No difference was found, but, with only six patients in each treated group, it is likely there was insufficient power to detect a true difference between the groups. Another study provided information on the post-treatment effects of pamidronate and concluded that, at least for 2 years after stopping medication, clinical effects on bone density remain. The potential for causing non-union has been a concern. One study systematically evaluated this and found no increased incidence of non-union; however, it probably lacked adequate power to exclude this complication. Little information is available on long-term outcomes, including side effects.

This body of evidence would be strengthened by a larger controlled trial, because many studies lacked adequate power to evaluate stated outcomes. Studies are needed to evaluate the impact of bisphosphonates in individuals with milder forms of OI and severe forms of OI that are not due to collagen mutations (e.g. types VII and VIII). Additional research is needed into treatment of infants. More studies evaluating medication choices, optimal dosing, duration of treatment, post-treatment impacts, and long-term side effects are necessary. Ideally, these studies should be performed in homogeneous groups (i.e. children of similar ages with the same pathophysiological cause for their bone fragility and similar levels of disease severity). Studies should include information on potential confounders such as intramedullary rodding and external bracing. To be accomplished, these studies would need to be multi-centered to allow recruitment of an adequate number of participants. Widespread use of bisphosphonate medication is already occurring, so it may be difficult to perform a randomized controlled trial in patients with moderate to severe OI with an untreated control group. Study designs assigning patients to different dosing regimens should be considered. Given the relatively small number of pediatric patients across studies and limited information regarding pregnancy outcomes in women treated with bisphosphonates, registries to monitor for rare side effects would be informative.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table SI: Osteogenesis imperfecta (OI) and other forms of genetic bone fragility: clinical features and pathophysiology

Table SII: All studies included in the systematic review of bisphosphonate treatments for osteogenesis imperfecta (OI)

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