Bisphosphonate therapy for osteogenesis imperfecta (Review)

Phillipi CA, Remmington T, Steiner RD

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Bisphosphonate therapy for osteogenesis imperfecta

Carrie A Phillipi[1], Tracey Remmington[2], Robert D Steiner[3]

[1]Pediatrics Department, Oregon Health & Science University, Portland, USA. [2]Institute of Child Health, University of Liverpool, Liverpool, UK. [3]Pediatrics Department, Head of Division of Metabolism, CDRC, Oregon Health & Science University, Portland, USA

Contact address: Carrie A Phillipi, Pediatrics Department, Oregon Health & Science University, 707 SW Gaines Street, Portland, Oregon, 97239-2901, USA. phillica@ohsu.edu. (Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.)

Cochrane Database of Systematic Reviews, Issue 1, 2009 (Status in this issue: *Unchanged*)

DOI: 10.1002/14651858.CD005088.pub2
This version first published online: 8 October 2008 in Issue 4, 2008.
Last assessed as up-to-date: 5 August 2008. (Help document - Dates and Statuses explained)

This record should be cited as: Phillipi CA, Remmington T, Steiner RD. Bisphosphonate therapy for osteogenesis imperfecta. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD005088. DOI: 10.1002/14651858.CD005088.pub2.

ABSTRACT

Background

In osteogenesis imperfecta (OI) a genetic defect in type I collagen results in multiple fractures with little or no trauma. Bisphosphonates are used to attempt to reduce these fractures.

Objectives

To assess the effectiveness and safety of bisphosphonates in increasing bone mineral density (BMD), reducing fractures and improving clinical function in people with OI.

Search strategy

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches, handsearches of journals and conference proceedings. We searched PubMed and major conference proceedings.

Register last searched: August 2008.

Selection criteria

Randomised and quasi-randomised controlled trials comparing bisphosphonates to placebo, no treatment, or comparator interventions in all types of OI.

Data collection and analysis

Two authors independently extracted data and assessed trial quality.

Main results

Eight studies (403 participants) were included. Data for oral bisphosphonates versus placebo could not be aggregated. A significant difference favouring bisphosphonates in fracture risk reduction and number of fractures was noted in one trial. No differences were reported in the remaining three trials. Two trials reported data for spine BMD; one found significantly increased lumbar spine density z scores at 12 months and one reported a significant increase in lumbar spine BMD at 12, 24 and 36 months; both favouring bisphosphonates. For intravenous bisphosphonates versus placebo, aggregated data from two trials showed no significant difference for

the number of participants with at least one fracture, RR 0.56 (95% CI 0.30 to 1.06). In the remaining trial no significant difference was noted in fracture incidence. For spine BMD, no significant difference was noted in the aggregated data from two trials, MD 9.96 (95%CI -2.51 to 22.43). In the remaining trial a significant difference in mean per cent change in spine BMD z score favoured intravenous bisphosphonates at 6 and 12 months. One trial compared oral versus intravenous bisphosphonates and found no differences in primary outcomes. Data describing growth, bone pain, and functional outcomes after bisphosphonate therapy were incomplete.

Authors' conclusions

Evidence suggests oral or intravenous bisphosphonates increase BMD in children and adults with OI. These were not shown to be different in their ability to increase BMD; it is unclear whether either treatment decreases fractures. Additional studies may determine whether bisphosphonates improve clinical status (reduce fractures and pain; improve growth and functional mobility) in this population. Optimal method, duration of therapy and long-term safety of bisphosphonate therapy requires further investigation.

PLAIN LANGUAGE SUMMARY

Bisphosphonate therapy for osteogenesis imperfecta

Osteogenesis imperfecta is an inherited disorder of type I collagen characterized by low bone mass, bone fragility, and fractures with minimal or no trauma. Treatment for the disorder is largely supportive, but recently bisphosphonate therapy has been employed in an attempt to increase bone mineral density and potentially reduce fracture incidence in affected individuals. We have included eight randomised trials, some placebo-controlled, some with a cross-over trial design, or both, in our review. Four trials report decreased fractures in some instances in those treated with bisphosphonates; however no significant difference was found in three other trials. Another trial demonstrated decreased vertebral and upper extremity but not lower extremity fractures. Each trial independently demonstrates significant improvements in bone mineral density after treatment with oral or intravenous bisphosphonates. Fracture incidence, bone pain, growth and quality of life indicators influenced by treatment with bisphosphonates warrant further investigation. Further investigation is needed to establish whether the improvements in bone mineral density translate into fracture reduction and functional improvements and to determine the long-term effectiveness and safety of their use.

BACKGROUND

Osteogenesis imperfecta (OI) is an inherited, primarily autosomal dominant condition, caused by mutations in the genes that encode type I collagen (Steiner 2005). OI (sometimes called brittle bone disease) is characterized by bone fragility, and predisposition to fractures in many cases with minimal or no trauma. Low bone mass is a common but not universal feature. In addition to multiple fractures, individuals with OI also commonly exhibit joint hypermobility, blue or grey-blue scleral colour, dentinogenesis imperfecta, and premature hearing loss (Cole 2002).

Type I collagen is the most abundant protein of bone and is also present in ligaments, tendons, dentin, sclera, and skin. Normal bone matrix is composed of 90% Type I collagen fibers and 10% non-collagenous proteins. These collagen fibers are usually oriented in a preferential direction with hydroxyapatite, [Ca10(PO4)6(OH)2], crystals located in the ground substance in and within these fibers. Hydroxyapatite crystals provide mechanical rigidity and strength to bone whereas collagen fibers provide resilience. Individuals with OI have less and/or poorer quality type-I collagen than unaffected people, causing their bones to deform and/or fracture. In 80% to 90% of people with OI, mutations in one of the two genes that encode type I collagen chains, COL1A1 and COL1A2, are found (Byers 1991).

The exact incidence of OI is unknown. Finnish data published in 2002 by Kuurila suggest 6 per 100,000 individuals are affected with the disorder (Kuurila 2002). Other studies suggest the incidence of severe OI may be as high as 1 in 25,000 live births (Byers 2000; Connor 1985; Orioli 1995). Parents with OI caused by collagen mutations have a 50% chance with each pregnancy of having an affected child and the majority of children with OI have inherited the disorder from a parent. However de novo mutations account for approximately 35% of children with OI (OIF 2008).

Prior to the availability of molecular genetic analyses, four major phenotypic classifications of OI were identified based on Sillence criteria which includes inheritance mode, clinical presentation and radiographic findings (Sillence 1979). Further refinement of these classifications was made with molecular genetic analyses (Byers 1991; Byers 1992; Glorieux 2000; OIF 2008; Steiner 2005) and recently, the addition of OI Types V, VI and VII have been proposed (Glorieux 2000). It is unclear whether OI Types V, VI, VII will be classified with OI in the future as these individuals do not have evidence of type I collagen mutations. The diagnosis is made by a combination of history including family history, clinical examination, and radiographic findings with genetic and/or biochemical testing available for diagnostic confirmation. The types of OI and their characteristics are listed in an additional table (Table 1).

Table 1. Classification of osteogenesis imperfecta

TYPE	GENETICS	CLINICAL FINDINGS
COLLAGEN DEFECTS		
OI type I	Autosomal dominant	Fractures with little or no limb deformity, blue sclera, normal stature, hearing loss, dentogenesis imperfecta rare
OI type II	Autosomal dominant	Lethal perinatal type: undermineralized skull, micromelic bones, "beaded" ribs on x-ray, bone deformity, platyspondyly
OI type III	Autosomal dominant (rarely autosomal recessive)	Progressive deforming type: limb deformities, sclera hue varies, very short stature, dentogenesis imperfect common
OI type IV	Autosomal dominant	Sclerae blue, grey, grey/blue, or white, mild/moderate limb deformity with fracture, variable short stature, dentogenesis imperfect common, some hearing loss

Table 1. Classification of osteogenesis imperfecta (*Continued*)

NEW TYPES BASED ON DISTINCT CLINICAL/HISTIOLOGIC/MOLECULAR GENETIC/BIOCHEMICAL FEATURES		
OI type V	Autosomal dominant	Similar to OI type IV plus calcification of interosseous membrane of forearm, radial head dislocation, and hyperplastic callus formation
OI type VI	Unknown	More fractures than OI IV, vertebral compression fractures, no dentogenesis imperfecta
OI CAUSED BY CRTAP MUTATIONS		
OI type VII	Autosomal recessive	Multiple fractures, bone deformity, mild short stature, bluish sclerae
OI CAUSED BY LEPRE MUTATIONS		
OI type VIII	Autosomal recessive	Very short stature, severe bone deformity, severe fractures with poor mineralization, barrel-shaped chest

OI: osteogenesis imperfecta

There is no cure for OI and no proven pharmacologic treatment. Therapy is largely supportive at present, and is varied and individualized depending upon OI severity, degree of impairment and age of the individual. Orthopedic management is paramount, and surgical intervention or bracing of lower limbs, or both, is often required. Physical and occupational therapy are mainstays of therapy. Pharmacologic agents including growth hormone, calcitonin, parathyroid hormone, sodium fluoride, vitamins and now bisphosphonates have been administered in attempts to reduce fractures and deformities in OI. Oral and intravenous bisphosphonates are currently the most promising therapy and are commonly used for OI, since uncontrolled clinical trials of these agents have shown improvements in bone mineral density (BMD) in people with OI (Glorieux 1998).

Bisphosphonates act by inactivating osteoclasts, the cells that break down bone tissue, thereby inhibiting bone resorption (Fisher 1999). There are two different types of bisphosphonates, nitrogenous and non-nitrogenous. Nitrogenous bisphosphonates disrupt osteoclast formation, survival and cytoskeletal dynamics. Non-nitrogenous bisphosphonates initiate osteoclast apoptosis. The bisphosphonates vary in their efficacy and absorption when taken orally, making direct comparison challenging. An additional table lists the currently available bisphosphonates (Table 2).

Table 2. Current bisphosphonates

Bisphosphonate	Mechanism of action	Route of admin
Alendronate* (Fosamax)	Nitrogenous	Oral
Clodronate (Bonefos)	Non-nitrogenous	Oral, intravenous
Etidronate (Didronel)	Non-nitrogenous	Oral
Ibandronate (Boniva)	Nitrogenous	Oral
Neridronate*	Nitrogenous	Intravenous
Olpadronate*	Nitrogenous	Oral, intravenous
Pamidronate* (Aredia)	Nitrogenous	Intravenous
Risendronate (Actonel)	Nitrogenous	Oral

Table 2. Current bisphosphonates (*Continued*)

Tiludronate (Skelid)	Non-nitrogenous	Oral
Zolendronate (Zometa, Reclast)	Nitrogenous	Intravenous

Nitrogenous bisphosphonates disrupt osteoclast formation, survival and cytoskeletal dynamics. They contain nitrogen (a colorless tasteless odorless element that as a diatomic gas is relatively inert and constitutes 78% of the atmosphere and that is a constituent of organic compounds found in all living tissues)

Non-nitrogenous bisphosphonates initiate osteoclast apoptosis.

Both types of bisphosphonates are widely used in post-menopausal women to treat osteoporosis where they have been shown to increase bone density, decrease bone turnover (Reid 2002) and reduce fractures (Black 1996). Although increases in BMD are not expected to alter the underlying defective Type I collagen in OI, it is anticipated that increased BMD might lead to decreased fracture rates analogous to bisphosphonate therapy in postmenopausal women with osteoporosis (Reid 2002). Animal models give reason for optimism as increases in BMD in a mouse model of OI are accompanied by decreases in fracture rate (Camacho 2001). Still caution is advised since the biology of OI differs from osteoporosis and improving bone density without altering resiliency may not lead to desired functional improvements (Marini 2003). A recent report of bisphosphonate-induced osteopetrosis validates these concerns (Whyte 2003). There is currently no consensus on the effectiveness and safety of these agents in the treatment of OI. Moreover, if a critical period exists in which to treat children and adults affected with OI with bisphosphonates, it as well as the duration of therapy are undefined, and bisphosphonates are not currently licensed for use in children in the United States. Children's natural proclivity towards increased BMD and growth, coupled with the tendency for decreased fractures with advancing age in children with OI make data comparison between adults and children difficult. Large, multi-center, randomised, placebo-controlled trials to better assess the specific effects of bisphosphonate therapy for OI are indicated. The goals for use of pharmacologic agents in OI include increased bone density as measured by dual-energy X-ray absorptiometry (DEXA), decreased fracture incidence, lessening of deformity, reduced pain, and improved growth and mobility.

OBJECTIVES

To assess the effectiveness and safety of bisphosphonates in increasing bone mineral density, reducing fractures and improving clinical function in people with osteogenesis imperfecta.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised trials, published or unpublished.

Types of participants

Children (defined as age 0 to 18 years) and adults with OI diagnosed using accepted diagnostic criteria, based on clinical or laboratory findings, or both. Individuals affected with all types of OI are included in this review.

Types of interventions

Use of bisphosphonates to improve BMD in OI compared to placebo, no treatment control group, or comparator interventions, such as sodium fluoride; testosterone; Vitamin C; Vitamin D; flavonoids; calcitonin; growth hormone; parathyroid hormone; and different formulations or treatment regimens of bisphosphonates.

Types of outcome measures

Primary outcomes

1. Fracture reduction (as numbers and rates)
2. Change in BMD as assessed by DEXA

Secondary outcomes

1. Change in biochemical markers of bone and mineral metabolism (e.g., bone alkaline phosphatase measurements)
2. Growth (z scores; vertebral heights)
3. Bone pain (as assessed by self-reported questionnaires of pain and analgesic use)
4. Quality of life (e.g., functional changes in mobility, strength, well-being and completion of activities of daily living (ADLs))
5. Lung function (e.g., pulmonary function testing)

Outcome data were grouped at six months and then annually. If outcome data had been recorded at other time periods, consideration was given to examining these as well.

Search methods for identification of studies

Electronic searches

Relevant internationally-based trials were identified from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register, compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of *The Cochrane Library*), quarterly searches of MEDLINE and the prospective handsearching of one journal - *Journal of Inherited Metabolic Disease*. Unpublished work was identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the CochraneCysticFibrosisandGeneticDisorders GroupModule.

PubMed and OVID MEDLINE searches from 1966 to March 2005 using MESH terms, osteogenesis imperfecta, randomised controlled trial, and Randomised Controlled Trials, were also carried out by the authors. The search strategies are listed in the additional tables (Table 3; Table 4).

Table 3. Search strategy - PubMed 1996 to June 2006

MESH terms
1. osteogenesis imperfecta (827)
2. randomized controlled trial or Randomized Controlled Trials (49443)
3. 1 and 2 (4)
4. from 4 keep (2)

Table 4. Search strategy - Ovid MEDLINE 1996 to June 2006

Search terms
1. osteogenesis imperfecta (163)
2. randomized controlled trial (11846)
3. Randomized Controlled Trials (11906)
4. Combine 1, 2, 3 (7)
5. From 7 keep 2 (2)

Date of the most recent search of the Group's Cystic Fibrosis and Genetic Disorders Group Inborn Errors of Metabolism Trials Register: August 2008.

Searching other resources

The major conference proceedings from the Osteogenesis Imperfecta Foundation national conference, 1995 to March 2005, and the American Society for Bone and Mineral Research annual meeting proceedings, 1996 to March 2005, were also hand searched in order to identify pertinent unpublished work. In addition, the authors contacted the pharmaceutical companies, whom manufacture bisphosphonates (November 2004), for information on any relevant RCTs, but only one manufacturer responded and no additional useful information was gathered from this attempt.

Data collection and analysis

Selection of studies

Two authors (CP and RS) read the papers identified by the review search strategy for relevancy and then assessed the trials for inclusion in the review based on the criteria outlined above. Important comparisons were identified within each class (e.g. oral versus intravenous bisphosphonates). If disagreement arose on the suitability of a trial for inclusion in the review or its quality, we reached a consensus by discussion.

Data extraction and management

Two authors independently extracted data using a structured form including date of publication, participant characteristics (especially demographics and type of OI), setting, detailed nature of intervention and control or, comparator, detailed nature of outcomes (i.e. bone density by DEXA, fractures, linear growth, bone turnover markers, bone pain and functional assessments).
Meta-analysis of the available data was limited due to the different agents used (oral versus intravenous bisphosphonates), different outcome measures, different populations (adults versus children), different reporting indices (z score versus t score versus total BMD), and variable inclusion of a placebo or control group.

Assessment of risk of bias in included studies

The authors based assessment of methodological quality of the trials on the method described by Jüni (Jüni 2001). In addition, they assessed generation of allocation sequence and concealment of allocation sequence as adequate, inadequate, or unclear. They also assessed each trial for the degree of blinding and whether an intention-to-treat analysis was undertaken. Furthermore they examined details of external validity (settings, treatment and measurement variables) and whether the number of participants lost to follow up or subsequently excluded from the trial was recorded (Jüni 2001). The authors have presented methodological quality ratings, and details as to why they assigned these ratings for each criterion, by individual trial in tabular form in the additional tables (Table 5). However, studies were not weighted on the basis of their assigned methodologic quality.

Table 5. Methodological quality of included studies

Study ID	Allocation conceal't	Randomization	Blinding	Type of analysis
Adami 2003	Method not stated.	Described as "randomized", but method not stated.	Prevalent vertebral fractures were identified and graded blindly by a semi-quantitative scale.	Per-protocol. Note: Intention-to-treat analysis was planned but not applied as all participants completed the treatment follow up.
Chevrel 2006	Researchers responsible for seeing participants allocated the next available number on entry into the trial.	Randomization was computer-generated.	Double-blinded (study personnel and participants), using a matched placebo.	Intention-to-treat.
DiMeglio 2006	Concealed via a nurse who assigned treatment.	Partially randomized. Participants were first stratified according to clinical severity of OI. Randomization was initially computer generated. Changes were made in assignment when participants had difficulties with intravenous	Not stated.	Not stated.

Table 5. Methodological quality of included studies (*Continued*)

		access or gastrointestinal complaints.		
Gatti 2005	Method not stated.	Described as "randomized" according to OI type and either an active or control group, but method not stated.	Not blinded.	Per-protocol. Note: Intention-to-treat analysis was planned but not applied as all participants completed the treatment follow up.
Glorieux 2004	Method not stated.	Stated as "randomized", no further information provided.	Stated as "double-blind", no further information provided.	Method not stated.
Letocha 2005	Method not stated.	Randomized by "randomly generated numbers".	Not blinded overall. Blinded for vertebral area and compression measures.	Per-protocol and Repeated Measures Model.
Sakkers 2004	Responsibility of a trial management department.	Randomization was by computer-generated random numbers.	Stated that researchers were blinded to treatment allocation.	Intention-to-treat.
Seikaly 2005	Pharmacist at institution assigned groups.	Randomization was computer generated (SAS 6.12). Included two period cross-over.	Double blind design.	Not stated.

Measures of treatment effect

For binary outcome measures the authors collected data on the number of participants for each outcome event and allocated treatment group. The authors calculated a pooled estimate of the treatment effect for each outcome across trials using risk ratios (RR) where appropriate.

For continuous outcomes, the authors recorded either the mean change from baseline for each group or mean post-treatment or intervention values and standard deviation or standard error for each group. The authors calculated a pooled estimate of treatment effect by calculating the mean difference (MD) and 95% confidence intervals (CIs) .

Unit of analysis issues

One cross-over trial was included in the review, data from this trial were treated as parallel data; we treated the results from the two periods as if they were independent (Seikaly 2005), Elbourne reports that using this approach is conservative, due to the fact that it ignores the within-patient correlation (Elbourne 2002).

For count data (number of fractures), the relative rate was calculated from the information given in the published papers from one trial using poisson regression (Sakkers 2004). These analyses were performed using the statistical software Stata.

Dealing with missing data

Data used in the review were sometimes estimated when only presented in graph form in the original papers (Chevrel 2006). Standard deviations were calculated when standard errors of the mean data were reported by the trialists (Seikaly 2005). Unpublished data on BMD were kindly provided by the trialists of the Adami and Gatti trials (Adami 2003; Gatti 2005).

Assessment of heterogeneity

For future updates when sufficient trials are included in the review, we plan to quantify the impact of statistical and clinical heterogeneity in the meta-analysis using a measure of the degree of inconsistency in the studies' results (Higgins 2003). This measure (I^2) describes the percentage of total variation across studies that are due to heterogeneity rather than chance (Higgins 2003). The

values of I^2 lie between 0% and 100%, and a simplified categorization of heterogeneity that we plan to use is of low (I^2 value of 25%), moderate (I^2 value of 50%), and high (I^2 value of 75%) (Higgins 2003).

Data synthesis

In this review we have analysed data using a fixed-effects model. However, if in future updates, if sufficient trials are included and if there is significant heterogeneity found, we plan to use a random-effects model of statistical analysis.

Subgroup analysis and investigation of heterogeneity

Where we find heterogeneity, and if we have sufficient trials included in a meta-analysis (i.e. four or more), we will investigate the possible causes further. Proposed subgroup analyses are by age (adults versus child); type of OI; and severity of disease (mild or severe).

Sensitivity analysis

When there are sufficient trials included in the review, a sensitivity analysis will be performed based on the methodological quality of the studies, including and excluding quasi-randomized trials.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
Please refer to the 'Characteristics of included studies' section and 'Table 6' for further details.

Table 6. Study comparison: outcome data reported by individual studies

Study ID	Biochemical markers	BMD	Fracture incidence	Growth	Bone pain	Quality of life
Adami 2003	Decrease in bone-specific alkaline phosphatase 20%, decrease 25% in serum sCTx, decrease 20% in urinary free-de-	Increase spine BMD 3.0 +/- 4.6%, hip 4.3 +/- 3.9% vs no significant change placebo.	14% decrease in rate of fracture.	Not addressed.	Not addressed.	Not addressed.

Table 6. Study comparison: outcome data reported by individual studies (*Continued*)

	oxypyridinoline in IV Neridronate group vs placebo.					
Chevrel 2006	Decrease in bone resorption markers (collagen peptides, osteocalcin) at one year. Alkaline phosphatase unchanged.	Increase spine BMD. Increase femur BMD. Effects seen primarily in first year of therapy.	No difference in vertebral or peripheral fracture rate. Not adequately powered.	Not addressed.	No difference in pain except an increase with alendronate at 36 month time point.	Not addressed.
DiMeglio 2006	Decrease in alkaline phsophatase and bone alkaline phosphatase; decrease in urine NTX/Cr.	Increase BMD, BMC and area z scores in both oral and IV therapy.	Decreased fracture incidence with time when both groups are combined.	Increase height and length combined group z scores compared to normal children.	Not addressed.	Not addressed.
Gatti 2005	Significant decrease in alkaline phosphatase from baseline. Groups did not differ.	Increase spine BMD in first 12 months, then groups were no longer different. BMD continued to be different from baseline. Initial increase (first 12 months) in height/projected lumbar spine area, followed by no change at 12 - 26 months.	Relative risk reduction 0.36% (CI, 0.15 - 0.87; P <0.02).	Initial increase (first 12 months) in height/projected lumbar spine area, followed by no change at 12 - 26 months.	Not addressed.	Not addressed.
Glorieux 2004	Decrease in urinary NTx - 62% in Alendronate group vs 32% in placebo group.	Increase spine BMD by 53% vs 16% increase with placebo. spine z score increased 1.3 SD vs no signif-	Not sufficiently powered.	Not addressed.	Non-significant trend towards pain reduction.	Not addressed.

Table 6. Study comparison: outcome data reported by individual studies (*Continued*)

		icant change in placebo.				
Letocha 2005	No significant change from baseline as measured at each infusion time.	Increase spine BMD in treatment group as compared to control group. Increases were seen in the first 12 months but no further increases were noted with extended therapy.	Decreased upper extremity fractures in the first year of treatment with no further decrease in the second year. No change in fracture incidence of lower extremity long bone fracture in the first or second year.	Growth rates were unchanged.	No difference in self-reported pain scores.	No difference in muscle strength or gross motor abilities.
Sakkers 2004	No significant change between groups.	Increase spine z score 1.67 SD vs no significant change placebo.	31% decrease in rate of fracture.	No significant change.	Not addressed.	No significant difference in mobility / ambulation; muscle strength or self care.
Seikaly 2005	Decrease in urinary NTX/Cr. No change in serum markers or other urinary markers of bone turnover.	Increase in BMD z score 0.89 with alendronate compared to -0.12 with placebo.	Non-significant trend toward decreased fractures.	Increased height z scores (0.41 vs 0.11) when alendronate is compared to placebo.	Decreased pain scores and decreased use of analgesia.	Improved well being scores. Increase in self care. No change in mobility.

IV: intravenous
NTX/Cr: N-linked telopeptides/creatinine
sCTx: serum cross-laps
vs: versus

Fourteen studies were identified and reviewed, of which eight (including 403 participants) RCTs met the inclusion criteria (Adami 2003; Chevrel 2006; DiMeglio 2006; Gatti 2005; Glorieux 2004; Letocha 2005; Sakkers 2004; Seikaly 2005). Three studies evaluated an oral bisphosphonate (Chevrel 2006; Glorieux 2004; Sakkers 2004), while four trials evaluated intravenous (IV) bisphosphonates (Adami 2003; Gatti 2005; Letocha 2005; Seikaly 2005). One trial compared oral to IV bisphosphonates (DiMeglio 2006). Six studies enrolled 293 children, one trial (Glorieux 2004) included participants up to 19 years, which we included as children (Glorieux 2004; Sakkers 2004; Gatti 2005; Letocha 2005; DiMeglio 2006; Seikaly 2005) and two studies enrolled 110 adults (Adami 2003; Chevrel 2006).

Six trials were excluded from the review (Antoniazzi 1996; Antoniazzi 2006; DiMeglio 2004; Gerber 1998; Granda 1977; Ward 2005). Four trials were not RCTs (Antoniazzi 1996; Antoniazzi 2006; DiMeglio 2004; Ward 2005); a further trial did not evaluate bisphosphonates, but rather long-leg braces (Gerber 1998); and the sixth trial studied pyrophosphate levels in OI disease severity rather than improvement in bone density or fracture reduction (Granda 1977).

An ongoing trial has been identified evaluating subcutaneous teriparatide in adults, which we plan to review in a future update (Teriparatide 2008). Results of a recently completed trial of pamidronate compared with zoledronic acid have yet to be

published but will be included in this review when available (Zoledronic Acid 2008).

Risk of bias in included studies

Despite differences in methodological quality, the results of each study were considered equally and were not weighted in the analysis. Further details of the methodological quality of the included studies can be found in the 'Additional table' section of the review (Table 5).

Allocation

Generation of the allocation sequence

The Letocha, Sakkers, Seikally and Cheverel trials were described as randomised, by computer-generated random numbers and were deemed adequate (Chevrel 2006; Letocha 2005; Sakkers 2004; Seikaly 2005).

The Adami and Glorieux trials were described as randomised, although no information on the randomised procedures used was given and the trials have therefore been rated as unclear (Adami 2003; Glorieux 2004). Similarly, the Gatti trial was described as a randomised controlled trial but the method was not fully described (Gatti 2005). Participants were assigned according to OI type to either an active or control group (rated as unclear) (Gatti 2005).

The DiMeglio trial was described as "partially randomised" in that initial randomisation was computer-generated and participants were stratified according to clinical severity of OI (rated adequate) (DiMeglio 2006).

Concealment of allocation

For the Adami, Glorieux, Gatti and Letocha trials, the method of allocation concealment was not stated and therefore rated as unclear (Adami 2003; Glorieux 2004; Gatti 2005; Letocha 2005).

For the Sakkers trial, generation of the randomisation sequence was done independently of the researchers by an outside group, therefore concealment was deemed adequate (Sakkers 2004). Similarly, for the Seikaly trial allocation was concealed by a pharmacist at the institution and was graded as adequate (Seikaly 2005).

For the Cheverel trial, allocation was concealed by giving the randomised list to the researchers who then assigned each new trial subject the subsequent number on the list (rated as adequate) (Chevrel 2006). For the DiMeglio trial, allocation concealment was ensured by a clinic nurse who assigned treatment (rated adequate) (DiMeglio 2006).

Blinding

Five trials were described as double-blinded (Glorieux 2004; Sakkers 2004; Letocha 2005; Seikaly 2005; Chevrel 2006). The Adami trial it was stated that "prevalent vertebral fractures were identified and graded blindly by a semi quantitative scale" (Adami 2003). In the Letocha trial, the investigators were stated as blinded to vertebral area/compression (Letocha 2005). The Seikaly trial was described as double-blinded (Seikaly 2005) and the Chevrel trial was described as double-blinded (study personnel and participants) (Chevrel 2006). The Gatti trial was not described as blinded (Gatti 2005).

Follow up and exclusions

In the Glorieux trial data were analysed by intention-to-treat. No more information was given in the abstract regarding withdrawals or dropouts as full publication is pending (Glorieux 2004). For the Sakkers trial, an intention-to-treat analysis was undertaken. Two participants (one placebo and one treatment) withdrew from the trial but were accounted for in the final analysis (Sakkers 2004). It was also reported that an intention-to-treat analyses were performed in the Cheverel trial (Chevrel 2006).

In the Adami trial, per-protocol analyses were performed; although intention-to-treat analyses were planned they were not applied as all participants completed the treatment follow up (Adami 2003). Similarly, in the Gatti trial intention-to-treat analyses were planned but not applied as all participants completed the treatment follow up (Gatti 2005).

In the Letocha trial a per-protocol and repeated-measures model was used (Letocha 2005).

For the Seikaly trial it is unclear whether intention-to-treat analyses were performed introducing potential attrition bias (Seikaly 2005).

The type of analysis performed is not stated for the DiMeglio trial (DiMeglio 2006), although changes in group assignment were made when participants had difficulty tolerating the assigned regimen.

Effects of interventions

As mentioned above, data were sometimes estimated when presented in graph form (Chevrel 2006). Standard deviations were calculated when standard errors of the mean data were reported by the trialists (Seikaly 2005). For the Adami and Gatti trials, the intervention groups each received treatment for 24 and 36 months respectively, and the "control" groups also began active therapy at 12 months for the remainder of each trial (Adami 2003; Gatti 2005). Data are reported in this review at the 6 and 12 month time-points for both trials where there is a comparison between intervention versus control (Adami 2003; Gatti 2005).

One cross-over trial was included in the review, data from this trial were treated as parallel data (Seikaly 2005). For count data (number of fractures), the relative rate was calculated from the information given in the published papers from three trials using poisson regression (Adami 2003; Gatti 2005; Sakkers 2004).

Oral bisphosphonates compared to placebo or no treatment control group

Four trials were included in this comparison (Chevrel 2006; Glorieux 2004; Sakkers 2004; Seikaly 2005).

Primary outcomes

1. Fracture incidence

Each of the four trials reported on this outcome (Chevrel 2006; Glorieux 2004; Sakkers 2004; Seikaly 2005). The Glorieux trial reported no statistically significant difference in fracture rate between alendronate and placebo, but the authors stated this end point was not adequately powered (Glorieux 2004). Full publication is pending. The Sakkers trial reported a 31% reduction in relative risk for fracture after treatment with oral olpadronate, and when analysed in the review this produced a hazard ratio of 0.69 (95% CI 0.52 to 0.91), Analysis 1.1 and a significantly decreased fracture number, relative rate (RR) 0.40 (95% CI 0.24 to 0.69), Analysis 1.2 (Sakkers 2004). Seikaly noted "a tendency to decrease the frequency of bone fractures" with alendronate versus placebo that did not reach significance (Seikaly 2005). Data cannot be entered into the meta-analysis for this cross-over trial as the total number of fractures (and not number of participants with one fracture or more) were reported across treatment groups. An additional trial also showed no significant difference in the number of fractures with alendronate compared to placebo, RR 0.97 (95% CI 0.48 to 1.95), Analysis 1.3 but was not adequately powered to detect differences in fracture rate (Chevrel 2006).

2. Change in BMD as assessed by DEXA

a. Mean % change in spine BMD

Each of the four trials reported on this outcome (Chevrel 2006; Glorieux 2004; Sakkers 2004; Seikaly 2005). Data are not available in an appropriate form to be entered into the meta-analyses for two trials (Glorieux 2004; Sakkers 2004). Data for two trials were presented as within-group changes (not presented in this review) showing significant improvements in the bisphosphonates group and non-significant changes in the placebo group (Glorieux 2004; Sakkers 2004). Seikaly found significantly increased lumbar spine density z scores at 12 months, in favour of alendronate, that were independent of order of administration of alendronate and placebo, MD 1.01 (95%CI 0.55 to 1.47), Analysis 1.4 (Seikaly 2005). Chevrel reported an increase in lumbar spine BMD throughout the three years of the trial. It was reported that the increase was much greater after the first 12 months, although this continued, without reaching a plateau to the end of treatment at 36 months; for lumbar spine at 12 months, MD 7.00 (95% CI 3.87 to 10.13); and at 24 months, MD 8.40 (95% CI 5.17 to 12.43); and at 36 months, MD 9.40 (95% CI 5.44 to 13.36), Analysis 1.5 (Chevrel 2006).

b. Mean % change in total femur BMD

One trial reported on this outcome (Chevrel 2006). The mean % change in total femur BMD were reported by Chevrel at 36 months, the increase in the alendronate group was significantly greater than that in the placebo group; total femur BMD, MD 3.00 (95% CI 2.73 to 3.27), Analysis 1.6 (Chevrel 2006).

Secondary Outcomes

1. Change in biochemical markers of bone and mineral metabolism and bone histology

The varied markers chosen for study in the included trials we reviewed prohibited direct comparison, but a narrative description of the findings are presented.

Each of the four trials reported on this outcome (Chevrel 2006; Glorieux 2004; Sakkers 2004; Seikaly 2005). Data for one trial were presented as within-group data and showed a significant decrease in N-telopeptide (NTx) in the bisphosphonate group as compared to the placebo group. No evidence of mineralization defect was found in either group, however within-group data are not presented (Glorieux 2004). Sakkers reported (in narrative format only) no significant change in urine or serum markers between the olpadronate and placebo groups (Sakkers 2004). Seikaly also found no change in serum or urinary markers of bone turnover between the alendronate and placebo groups. However, since data for this cross-over trial were presented separately by treatment arm for each of the four arms of the trial, we were unable to analyse this as if it were a parallel trial as planned (*See*: Unit of analysis issues) (Seikaly 2005). A decrease in some bone resorption markers (collagen peptides, osteocalcin) with alendronate administration was noted by Chevrel while alkaline phosphatase levels were unchanged (Chevrel 2006).

2. Growth

Two trials reported on this outcome (Sakkers 2004; Seikaly 2005). Sakkers narratively reported no differences in seated height or radiographic assessments of lumbar vertebral height between olpadronate and placebo at 24 months follow up (Sakkers 2004). Seikaly noted a significant increase in height growth z scores in response to 12 months of alendronate therapy, MD 0.50 (95% CI 0.04 to 0.96), Analysis 1.7 (Seikaly 2005). This outcome was not addressed in the remaining two trials (Chevrel 2006; Glorieux 2004).

3. Bone pain

Three trials reported on this outcome (Chevrel 2006; Glorieux 2004; Seikaly 2005). Glorieux narratively reported a non-significant trend towards reduction of bone pain (Glorieux 2004). For the alendronate group, a significant decrease in pain scores and analgesic use at 12 months were reported by Seikaly, MD -3.63 (95% CI -5.17 to -2.09), MD -2.00 (95% CI -3.57 to -0.43), respectively Analysis 1.8 (Seikaly 2005). Here, the interaction of treatment and order were not significant indicating that differences found between alendronate and placebo were not explained

by order of administration. Chevrel narratively reported that the pain score was similar in both groups from 0 to 30 months and reported end of trial data that showed an increase at 36 months with alendronate, MD 1.30 (95% CI 0.14 to 2.46), Analysis 1.8 (Chevrel 2006). Bone pain was not evaluated by Sakkers (Sakkers 2004).

4. Quality of life

Each of the four included trials evaluated at least one quality of life outcome (Chevrel 2006; Glorieux 2004; Sakkers 2004; Seikaly 2005). Seikaly reported a significant increase in well-being as assessed by scored participant recall, MD 3.19 (95% CI 2.25 to 4.13), Analysis 1.10; improved self care skills/ADLs (assessed by PEDI, a validated measurement tool) with alendronate versus placebo, MD 3.58 (95%CI 1.06 to 6.10), Analysis 1.11; but no improvements in mobility as assessed by WeeFIM (a validated measurement tool for transfers, locomotion, access to stairs), MD 0.79 (95%CI -3.31 to 4.89), Analysis 1.12 (Seikaly 2005). In contrast, Sakkers compared olpadronate to placebo and narratively reported that there were no changes in functional outcomes as assessed by PEDI, nor did the authors find changes in grip or hip flexor strength. Mobility as assessed by another validated scale (Bleck) was also not improved when compared to placebo controls (Sakkers 2004). These functional outcomes were not addressed in other included studies (Chevrel 2006; Glorieux 2004). Chevrel was the only trial to assess hearing and did not find any difference (as assessed by Rinne testing %) with alendronate administration; MD -0.10 (95% CI -2.88 to 2.68), Analysis 1.13 (Chevrel 2006).

5. Lung function

None of the included trials reported on this outcome (Chevrel 2006; Glorieux 2004; Sakkers 2004; Seikaly 2005).

IV Bisphosphonates compared to placebo or no treatment control group

Three trials were included in this comparison (Adami 2003; Gatti 2005; Letocha 2005).

Primary outcomes

1. Fracture incidence

Each of the included trials reported on this outcome (Adami 2003; Gatti 2005; Letocha 2005). For the Adami and Gatti trials, data on the number of participants with at least one fracture were obtained from the primary investigators, there was no significant difference between the treatment and control groups, RR 0.56 (95% CI 0.30 to 1.06), Analysis 2.1 (Adami 2003; Gatti 2005). Data were also obtained on the total number of fractures amongst participants for the treatment and control groups and these were 1/31 and 2/15 (respectively) for the Adami trial and 13/42 and 18/22 for the Gatti trial (Adami 2003; Gatti 2005). For the Letocha trial the incidence of fractures of the lower and upper extremities at 12 months did not change significantly between the pamidronate and placebo groups from baseline, MD -0.11 (95% CI -0.96 to 0.74); MD -0.22 (95% CI -0.67 to 0.23), respectively, Analysis 2.2, Analysis 2.3 (Letocha 2005).

2. Change in BMD as assessed by DEXA

a. Mean % change in spine BMD

Each of the included trials reported on this outcome (Adami 2003; Gatti 2005; Letocha 2005). Adami reported BMD at 6 month intervals from 6 to 24 months. In this trial, the intervention group received neridronate for 24 months and the "control" group began therapy at 12 months which continued for 12 months. We therefore report data here for the 6 and 12 month time points to compare intervention versus no treatment. (Adami 2003). When summary statistics from these two studies were calculated, no significant differences between treatment and control groups were noted in spine BMD at 6 months, MD 9.96 (95% CI -2.51 to 22.43) or at 12 months, MD 14.68 (95% CI -6.08 to 35.45), Analysis 2.4 (Adami 2003). Letocha investigated the mean per cent change in spine BMD z score and found significant increases with IV palmidronate at 6 months, MD 21.59 (95% CI 5.79 to 37.39) and 12 months, MD 25.60 (95% CI 11.48 to 39.72), Analysis 2.5 (Letocha 2005).

b. Mean % change in hip BMD

Two of the included trials reported on this outcome (Adami 2003; Gatti 2005). Adami and Gatti reported data on total hip BMD at 6 and 12 months. No significant differences were noted when hip BMD data from these trials were combined, MD 6.16 (95% CI -3.57 to 15.90) and MD 11.27 (95% CI -3.69 to 26.22) respectively, Analysis 2.6 (Adami 2003; Gatti 2005).

We note for both mean per cent change in spine and hip BMD for the Adami and Gatti trials that there are large differences in the standard deviations reported for each of these two trials and whilst clinically it is appropriate for these trials to be combined, we plan to investigate this heterogeneity further once more trials are included (Adami 2003; Gatti 2005).

Secondary Outcomes

1. Change in biochemical markers of bone and mineral metabolism and bone histology

Two trials reported on this outcome (Adami 2003; Gatti 2005). Information was provided narratively within the text for each trial. Adami reported a decrease in: bone specific alkaline phosphatase (BSAP); serum C-telopeptide (sCTx); and urinary free-deoxy pyridinoline (ufDPD) in the neridronate group (within group

data not presented) (Adami 2003). In the Gatti trial, significant decreases in alkaline phosphatase were found with IV administration of neridronate in children (Gatti 2005).

2. Growth

One trial reported on this outcome (Letocha 2005). No significant improvements in growth rate were noted by Letocha looking at IV pamidronate versus control, MD 1.07 (95% CI -2.24 to 4.38), Analysis 2.7 (Letocha 2005). Growth was not measured in the remaining trials of IV bisphosphonates (Adami 2003; Gatti 2005).

3. Bone pain

One trial reported on this outcome (Letocha 2005). No changes in self-reported bone pain on a self-evaluation four-point scale were found by Letocha, MD -0.11 (95% CI -0.83 to 0.61), Analysis 2.8 (Letocha 2005). Bone pain was not addressed by the remaining two trials using IV bisphosphonates (Adami 2003; Gatti 2005).

4. Quality of life

One trial reported on this outcome (Letocha 2005). Letocha investigated muscle strength and gross motor function (using BAMF (Brief Assessment of Motor Function), a 10-point gross motor assessment tool) (Letocha 2005). No differences in muscle strength or functional mobility were noted between the IV pamidronate and control groups during treatment, MD -3.18 (95% CI -18.97 to 12.61); MD -0.80 (95% CI -2.42 to 0.82), respectively Analysis 2.9, Analysis 2.10 (Letocha 2005). Outcomes reflecting quality of life were not evaluated in the remaining IV bisphosphonates trials (Adami 2003; Gatti 2005).

5. Lung function

None of the included trials reported on this outcome (Adami 2003; Gatti 2005; Letocha 2005).

Oral versus IV bisphosphonates

One trial was included in this comparison (DiMeglio 2006).

Primary outcomes

1. Fracture incidence

DiMeglio reported annualised fracture rates and found no difference between oral alendronate and intravenous pamidronate treatment groups, MD 0.50 (95% CI -0.64 to 1.64) Analysis 3.1 (DiMeglio 2006)

2. Change in BMD as assessed by DEXA

DiMeglio did not find a difference in BMD when they compared oral to IV therapy at 12 months, MD 0.30 (95% CI -1.11 to 1.71) and 24 months, MD 0.20 (95% CI -1.32 to 1.72), Analysis 3.2 (DiMeglio 2006).

Secondary Outcomes

1. Change in biochemical markers of bone and mineral metabolism and bone histology

DiMeglio reported that there were no significant differences in response between the two treatment groups at 4, 12, or 24 months. Data were reported for the 4 and 24 months time-periods for change in alkaline phosphonate (IU/L)) at four months, MD -12.00 (95% CI -86.09 to 62.09) and 12 months, MD -35.00 (95% CI -115.36 to 45.36); change in bone alkaline phosphonate (IU/L) at four months, MD 5.00 (95% CI -22.36 to 32.36) and 12 months, MD -12.00 (95% CI -39.78 to 15.78); and change in NTX/Cr (nMBCE/mM) at four months, MD -108.00 (95% CI -300.32 to 84.32) and 12 months, MD -111.00 (95% CI -269.38 to 47.38) (DiMeglio 2006).

2. Growth

DiMeglio found no significant difference in height compared to baseline in the oral or IV groups (within-group data) (DiMeglio 2006).

3. Bone pain

Bone pain was not investigated by DiMeglio (DiMeglio 2006).

4. Quality of life

Quality of life indicators were not addressed by DiMeglio (DiMeglio 2006).

5. Lung function

Lung function was not investigated by DiMeglio (DiMeglio 2006).

DISCUSSION

Eight studies were included in this review (Adami 2003; Chevrel 2006; DiMeglio 2006; Gatti 2005; Glorieux 2004; Letocha 2005; Sakkers 2004; Seikaly 2005). Six studies enrolled children (DiMeglio 2006; Gatti 2005; Glorieux 2004; Letocha 2005; Sakkers 2004; Seikaly 2005) and two enrolled adults (Adami 2003; Chevrel 2006). To varying degrees, these studies investigated changes in BMD, fracture rate, markers of bone turnover, growth, pain and quality of life with bisphosphonate therapy. For a summary of outcomes reported, see 'Additional tables' (Table 6).

All studies assessing BMD independently reported significant increases after treatment with either oral or IV bisphosphonate

and at separate sites (spine, hip, femur) (Adami 2003; Chevrel 2006; DiMeglio 2006; Gatti 2005; Glorieux 2004; Letocha 2005; Sakkers 2004; Seikaly 2005). However, it is difficult to compare these trials directly as different populations were included (adults versus children; for accurate comparisons children cannot be compared to adults due to high bone turnover during childhood and adolescence and open epiphyses). Additionally, different reporting indices were used (z score versus t score versus total BMD). As previously mentioned, the expected growth and BMD increases in children and adolescents with OI, coupled with their tendency for decreased fractures, make data comparison challenging. Significant gains in spine and hip BMD were not seen with IV bisphosphonate administration at 6 and 12 months with combined summary statistics, indicating need for continued rigorous study (Adami 2003; Gatti 2005). Interestingly, multiple studies reported the largest gains in BMD in the first year of therapy (Adami 2003; Chevrel 2006; Gatti 2005; Letocha 2005) and gains in BMD were independent of administration of therapy in a placebo-controlled cross-over trial (Seikaly 2005). These data possibly argue for short-course bisphosphonate therapy but further evaluation is certainly indicated. When oral and IV bisphosphonates were directly compared, both significantly increased spine BMD z scores at 12 and 24 months, but there were no differences in BMD between groups when route of administration was considered (DiMeglio 2006, Analysis 3.2).

The combined data analyses supporting a change in fracture incidence after bisphosphonate therapy are less straightforward. Adami reported a 14% reduction of fractures after adults were treated with IV neridronate (Adami 2003). Sakkers found a 31% reduction in the relative risk of fracture of long bones after treatment with oral olpadronate in children affected with OI (Sakkers 2004). Relative risk of fracture was also reduced (RR reduction 0.36%) in another trial (Gatti 2005). Seikaly noted a non-significant trend toward decreased fractures (Seikaly 2005). DiMeglio found no differences in fracture incidence with oral versus IV bisphosphonate administration and noted a decreased fracture incidence with time but only when oral and IV groups were combined (DiMeglio 2006). Letocha found decreased upper extremity but not lower extremity fracture rates in the first year of therapy but no further increases were noted when therapy was extended (Letocha 2005). Chevrel found no difference in vertebral or peripheral fracture rates but was not adequately powered to detect a difference (Chevrel 2006). The Glorieux trial was also not sufficiently powered to detect a change in fracture rate but found no difference in fracture with bisphosphonate administration (Glorieux 2004). When we further analysed the number of participants with at least one fracture, we found no difference in fractures in patients treated with IV neridronate compared to the control population (Adami 2003, Gatti 2005, Analysis 2.1). These studies employed retrospective fracture recall as a method for comparison, leading to potential recall bias. The number of patients randomised versus lost to follow up was also unclear in one trial (Adami 2003). Consideration of these factors, in addition to the aforementioned natural tendency toward reduction in fractures with age highlight the importance of prospective, placebo-controlled evaluation of bisphosphonates and fracture incidence in children.

Eight studies measured serum or urine markers of bone turnover, or both. Six studies reported decreases in serum (Adami 2003; Chevrel 2006; DiMeglio 2006; Gatti 2005;) or urine type I collagen byproducts (Adami 2003; DiMeglio 2006; Glorieux 2004; Seikaly 2005) whereas two trials reported no statistical difference in biochemical markers of bone turnover between treatment and control groups or from baseline (Letocha 2005; Sakkers 2004). The clinical significance and utilization of these biochemical markers of bone turnover are not universally utilized, however, the assumption is they act as a proxy for efficacy of therapy. The varied markers chosen for study in the trials we reviewed prohibited direct comparison, but more systematic study of these markers could assist investigators in assessing response to individual bisphosphonates and their dosing, as well as participant compliance or concordance, or both, with therapy.

It is uncertain whether bisphosphonate therapy increases growth as assessed by four studies included in this review. Seikaly reported increased height z scores with oral bisphosphonates (Seikaly 2005). Growth as assessed by height and length combined z scores compared to normal children was increased in another trial when children receiving oral and IV therapies were combined (DiMeglio 2006). Letocha found growth rates were unchanged by bisphosphonate therapy (Letocha 2005). Seated height and vertebral height were also not different in the treatment versus placebo group of another trial (Sakkers 2004). It is not within the scope of this review to distinguish between bisphosphonate responsiveness in different OI types, however it is interesting to note that milder forms of OI showed more improvements in growth and BMD in at least one trial (DiMeglio 2006).

It is important to determine whether bisphosphonate administration translates into functional changes and bone pain and quality of life were addressed in several studies. Decreased pain scores and decreased analgesic use were reported in one trial (Seikaly 2005) and Glorieux found a non-significant reduction in reported bone pain (Glorieux 2004). However, Letocha and Chevrel found no difference in self-reported pain scores, with the exception of increased pain with bisphosphonates at one time point measured (36 months; Chevrel 2006). When the authors re-evaluated this difference, they found it significant in the intention-to-treat analysis, but not in the per protocol analysis. Seikaly found improved well-being scores and increases in self care abilities but no change in mobility (Seikaly 2005). However, Sakkers found no changes in self-care abilities, nor did the authors find changes in strength or mobility when compared to placebo-controls (Sakkers 2004). Additionally, no differences in muscle strength or gross motor abilities were found in another trial (Letocha 2005). Chevrel was the only trial to assess hearing and found no change in Rinne testing with

bisphosphonate therapy (Chevrel 2006). Taken together, the data presented here do not support consistent improvements in these quality of life indicators with bisphosphonate administration.

RCTs including IV and oral bisphosphonate use were included in this review. Mean bisphosphonate oral bioavailability (alendronate) in children is comparable to that found in adult studies, with approximately 50% localizing to bone (Ward 2005). However, individual oral bioavailability of alendronate varies as much as ten-fold and could contribute to variable responsiveness (Ward 2005). We did not separately assess different bisphosphonate preparations although we have distinguished between oral and IV therapy. Different preparations potentially underlie heterogeneous responses in individual participants. Additionally, although we made no attempt to distinguish between OI type and response to bisphosphonate therapy, it is entirely plausible different OI types will respond to therapy differently as one trial suggests (DiMeglio 2004).

Although specific data were not extracted, bisphosphonate therapy administered for 1 to 3 years appears to be safe and well-tolerated in the adults and children treated here. Adverse effects of bisphosphonates are few and minor in this population (gastrointestinal complaints, fever, headache, small decreases in lymphocyte counts) and the drug is generally well-tolerated (DiMeglio 2006; Letocha 2005; Ward 2005;). Flu-like symptoms described as "acute phase reactions" were common with IV administration of bisphosphonates, particularly with the first infusion (DiMeglio 2006; Letocha 2005) but rarely contributed to trial withdrawal. Intravenous access was difficult in one trial not included in this review where four of nine children less than three years required central line placement for intravenous bisphosphonate administration (DiMeglio 2004). Intravenous access was otherwise not reported to be problematic in children or adults. Clinical or laboratory evidence of hypocalcemia was not found (Seikaly 2005; Ward 2005) nor was evidence or hepatic or renal dysfunction or changes in nephrocalcinosis as measured by ultrasound (Sakkers 2004; Seikaly 2005). The optimal method, dose, initiation and duration of therapy remain unclear. However, IV neridronate has been administered to infants with OI as young as neonates with reported improved growth and lowered fracture incidence (Antoniazzi 2006). A more extensive safety review of bisphosphonate use in children with low BMD and fragility fractures in juvenile idiopathic arthritis has been recently published (Thornton 2006).

We could not identify any RCTs using pharmacological agents other than bisphosphonates in OI. It seems that recent focus of pharmacological treatment for OI has been on bisphosphonates. For a review of pharmacological agents used prior to 1991, see Byers (Byers 1992). The authors are also aware of one ongoing RCT evaluating subcutaneous teriparatide in adults and this trial will also be reviewed in a future update (Teriparatide 2008). The results of a recently completed trial of pamidronate compared with zoledronic acid have not yet been published (Zoledronic Acid 2008).

AUTHORS' CONCLUSIONS

Implications for practice

The results from the included studies provide evidence, albeit in a relatively small population, that there is significant improvement in BMD in individuals affected with OI when treated with either oral or IV bisphosphonates. It remains to be seen whether this increase in BMD is a surrogate marker for fracture reduction and clinical functional improvement. Additionally, the long-term safety of bisphosphonates in OI, particularly when used in children, and the effects of bisphosphonates on fracture and perioperative bone healing have not been sufficiently evaluated. Effects of bisphosphonates on fracture incidence, growth, bone deformity, mobility, and pain have not yet been adequately studied.

Implications for research

A number of questions concerning bisphosphonate therapy in children and adults with osteogenesis imperfecta remain unanswered:

1. Do increases in BMD convincingly translate into fracture reduction and functional improvement?

Additionally, it remains unclear whether:

1. Bisphosphonates are equally safe and effective in children and adults. What are the long-term effects of osteoclast inhibitors like bisphosphonates on the immature growing skeleton? Will they be licensed for use in children (www.fda.gov/cder/foi/esum/2003/20560se1-038BPCA.PDF)?

2. There are differences in the safety or efficacy of IV versus oral bisphosphonates. Are there differences in safety and efficacy of individual bisphosphonates in OI? The optimal method, dosage, length of therapy as well as optimal therapeutic window also warrant investigation.

3. The efficacy of bisphosphonates in increasing BMD will be confirmed in larger studies, and with more heterogeneous participants. Does the efficacy of bisphosphonates differ by OI clinical type or mutation type, and are bisphosphonates useful in OI types V, VI, and VII?

4. Bisphosphonates in OI delay or impair fracture healing, or perioperative bone healing?

Well-designed, adequately-powered, placebo-controlled RCTs assessing the longitudinal effects of bisphosphonates on BMD, fracture reduction and healing, and changes in quality of life indicators such as function and pain should be studied in both children and adults with OI. These studies should be prospective, longitudinal, double-blinded, using comparable assessments of change

including z scores for BMD and growth, as well as validated assessments measuring pain and quality of life outcomes. Quality of life outcomes should be broadened to other include other factors important to people with OI, such as hearing and dentition and biochemical markers of bone turnover should be carefully assessed to determine if they are an adequate proxy for dose efficacy and subject concordance with therapy. Spontaneous versus non-spontaneous fractures should be investigated in these trials as well as bone healing after fractures and operative intervention with bisphosphonates.

ACKNOWLEDGEMENTS

Janet Reeder was the lead author on the published protocol and her valuable contributions to this review are gratefully acknowledged. The authors acknowledge the Osteogenesis Imperfecta Foundation for providing useful background information and for their encouragement. We also thank the investigators of specific trials (Adami 2003 and Gatti 2005) for providing unpublished data.

REFERENCES

References to studies included in this review

Adami 2003 *{published and unpublished data}*

* Adami S, Gatti D, Colapietro F, Fracassi E, Braga V, Rossini M, et al.Intravenous neridronate in adults with osteogenesis imperfecta. *Journal of Bone and Mineral Research* 2003;**18**(1):126–30.

Gatti D, Viapiana O, Lippolis I, Braga V, Prizzi R, Rossini M, et al.Intravenous bisphosphonate therapy increases radial width in adults with osteogenesis imperfecta. *Journal of Bone and Mineral Research* 2005;**20**(8):1323–6.

Chevrel 2006 *{published data only}*

Chevrel G, Schott AM, Fontanges E, Charrin JE, Lina-Granade G, Duboeuf F, et al.Effects of oral alendronate on BMD in adult patients with osteogenesis imperfecta: a 3-year randomized placebo-controlled trial.. *Journal of Bone and Mineral Research* 2006;**21**(2): 300–6.

DiMeglio 2006 *{published data only}*

Dimeglio LA, Ford L, McClintock C, Peacock M. A comparison of oral and intravenous bisphosphonate therapy for children with osteogenesis imperfecta. *Journal of Pediatric Endocrinology and Metabolism* 2005;**18**(1):43–53.

* DiMeglio LA, Peacock M. Two-year clinical trial of oral alendronate versus intravenous pamidronate in children with osteogenesis imperfecta. *Journal of Bone and Mineral Research* 2006;**21**(1):132–40.

Gatti 2005 *{published and unpublished data}*

Gatti D, Antoniazzi F, Prizzi R, Braga V, Rossini M, Tato L, et al.Intravenous neridronate in children with osteogenesis imperfecta: A randomized controlled study. *Journal of Bone and Mineral Research* 2005;**20**(5):758–63.

Glorieux 2004 *{published data only}*

Glorieux FH, Rauch F, Ward LM, Smith P, Verbruggen N, Heyden N, et al.Alendronate in the treatment of pediatric osteogenesis imperfecta [abstract]. *Journal of Bone and Mineral Research* 2004;**20** (Suppl):1043.

Letocha 2005 *{published data only}*

Letocha AD, Cintas HL, Troendle JF, Reynolds JC, Cann CE, Chernoff EJ, et al.Controlled trial of pamidronate in children with types III and IV osteogenesis imperfecta confirms vertebral gains but not short-term functional improvement. *Journal of Bone and Mineral Research* 2005;**20**(6):977–86.

Sakkers 2004 *{published data only}*

Sakkers R, Kok D, Engelbert R, Van Dongen A, Jansen M, Pruijs H, et al.Skeletal effects and functiona outcome with olpadronate in children with osteogenesis imperfecta: a 2-year randomised placebo-controlled study. *Lancet* 2004;**363**(9419):1427–31.

Seikaly 2005 *{published data only}*

Seikaly MG, Kopanati S, Salhab N, Waber P, Patterson D, Browne R, et al.Impact of alendronate on quality of life in children with osteogenesis imperfecta. *Journal of Pediatric Orthopaedics* 2005;**25** (6):786–91.

References to studies excluded from this review

Antoniazzi 1996 *{published data only}*

Antoniazzi F, Bertoldo F, Mottes M, Valli M, Sirpresi S, Zamboni G, et al.Growth hormone treatment in osteogenesis imperfecta with quantitative defect of type I collagen synthesis. *Journal of Pediatrics* 1996;**129**(3):432–9.

Antoniazzi 2006 *{published data only}*
Antoniazzi F, Zamboni G, Lauriola S, Donadi L, Adami S, Tato L. Early bisphosphonate treatment in infants with severe osteogenesis imperfecta. *Journal of Pediatrics* 2006;**149**(2):174–9.

DiMeglio 2004 *{published data only}*
DiMeglio LA, Ford L, McClintock C, Peacock M. Intravenous pamidronate treatment of children under 36 months of age with osteogenesis imperfecta. *Bone* 2004;**35**(5):1038–45.

Gerber 1998 *{published data only}*
Gerber LH, Binder H, Berry R, Siegel KL, Kim H, Weintrob J, et al.Effect of withdrawal of bracing in matched pairs of children with osteogenesis imperfecta. *Archives of Physical Medicine and Rehabilitation* 1998;**79**(1):46–51.

Granda 1977 *{published data only}*
Granda JL, Falva KA, Bullough PG. Phyrophosphate levels and magnesium oxide therapy in osteogenesis imperfecta. *Clinical Orthopaedics and Related Research* 1977;**Jul-Aug**(216):228–31.

Ward 2005 *{published data only}*
Ward LM, Denker AE, Porras A, Shugarts S, Kline W, Travers R, et al.Single-dose pharmacokinetics and tolerability of alendronate 35- and 70-milligram tablets in children and adolescents with osteogenesis imperfecta type I. *Journal of Clinical Endocrinology and Metabolism* 2005;**90**(7):4051–6.

References to ongoing studies

Teriparatide 2008 *{unpublished data only}*
A study to assess the effectiveness of teriparatide (FORTEO) for increasing bone mass and improving bone structure in adults affected with OI.Study ID numbers: IBMD-OI.ClinicalTrials.gov identifier NCT00063479.. Ongoing study 05/03/2005..

Zoledronic Acid 2008 *{unpublished data only}*
Bisphosphonate treatment of OI.Study ID numbers: CZOL446H2202.ClinicalTrials.gov identifier NCT00063479.. Ongoing study June 2003..

Additional references

Black 1996
Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al.Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996; **348**(9041):1535–41.

Byers 1991
Byers PH, Wallis GA, Willing MC. Osteogenesis imperfecta: translation of mutation to phenotype. *Journal of Medical Genetics* 1991; **28**(7):433–42.

Byers 1992
Byers PH, Steiner RD. Osteogenesis imperfecta. *Annual Review of Medicine* 1992;**43**:269–82.

Byers 2000
Byers PH. Osteogenesis imperfecta: perspectives and opportunities. *Current Opinion in Pediatrics* 2000;**12**(6):603–9.

Camacho 2001
Camacho NP, Raggio CL, Doty SB, Root L, Zraick V, Ilg WA, et al.A controlled study of the effects of alendronate in a growing mouse model of osteogenesis imperfecta. *Calcified Tissue International* 2001; **69**(2):94–101.

Cole 2002
Cole WG. Advances in Osteogenesis Imperfecta. *Clinical Orthopaedics and Related Research* 2002;**401**:6–16.

Connor 1985
Connor JM, Connor RA, Sweet EM, Gibson AA, Patrick WJ, McNay MB, et al.Lethal neonatal chondrodysplasias in the West of Scotland 1970-1983 with a description of a thanatophoric, dysplasialike, autosomal recessive disorder, Glasgow variant. *American Journal of Medical Genetics* 1985;**22**(2):243–53.

Elbourne 2002
Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Fisher 1999
Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, et al.Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro [abstract]. *Proceedings of the National Academy of Sciences of the United States of America* 1999;**96**:133–8.

Glorieux 1998
Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *New England Journal of Medicine* 1998;**339** (14):947–52.

Glorieux 2000
Glorieux FH, Rauch F, Plotkin H, Ward L, Travers R, Roughley P, et al.Type V osteogenesis imperfecta: a new form of brittle bone disease. *Journal of Bone and Mineral Research* 2000;**15**(9):1650–8.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Jüni 2001
Jüni T, Altman, DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;**323** (7303):42–6.

Kuurila 2002
Kuurila K, Kaitila I, Johansson R, Grenman R. Hearing loss in Finnish adults with osteogenesis imperfecta: a nationwide survey. *The Annals of Otology, Rhinology, and Laryngology* 2002;**111**(10): 939–46.

Marini 2003
Marini JC. Do bisphosphonates make children's bones better or brittle?. *New England Journal of Medicine* 2003;**349**(5):423–6.

OIF 2008
Osteogenesis Imperfecta Foundation. Facts about Osteogenesis Imperfecta. www.oif.org (accessed August 2008).

Orioli 1995
Orioli IM, Castilla EE, Scarano G, Mastroiacovo P. Effect of paternal age in achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta. *American Journal of Medical Genetics* 1995;**59**(2):209–17.

Reid 2002
Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, et al.Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *New England Journal of Medicine* 2002; **346**(9):653–61.

Sillence 1979
Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *Journal of Medical Genetics* 1979;**16**(2):101–16.

Steiner 2005
Steiner RD, Pepin MG, Byers PH. Gene Reviews; Osteogenesis Imperfecta. www.genetests.org (accessed 28 January 2005).

Thornton 2006
Thornton J, Ashcroft DM, Mughal MZ, Elliott RA, O'Neill TW, Symmons D. Systematic review of effectiveness of bisphosphonates in treatment of low bone mineral density and fragility fractures in juvenile idiopathic arthritis. *Archives of Disease in Childhood* 2006; **91**(9):753–61.

Whyte 2003
Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S. Bisphosphonate-induced osteopetrosis. *New England Journal of Medicine* 2003;**349**(5):457–63.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adami 2003

Methods	Single center, double-blinded, placebo-controlled RCT. Parallel for 1 year then the control group crossed over for an additional year.
Participants	46 adults (23 male) were randomized. Mean age (range): 34.9 years (21 to 50 years). Any type of OI.
Interventions	IV neridronate versus no treatment. Dosage: 100 mg diluted in 250 ml of saline solution infused intravenously in 30 min every 3 months. Study period: 24 months. Groups: 31 participants in the neridronate group versus 15 in the control group. After 12 months the control group also received intervention (neridronate). All participants seen at 3-month intervals, but full clinical evaluation including bone densitometry measurements by DXA and fasting serum and urinary (second morning voiding) biochemistry was obtained per-protocol every 6 months. Radiographs of the spine (anteroposterior and lateral views) were obtained at baseline and after 12 and 24 months.

Adami 2003 (*Continued*)

Outcomes	Fractures, spine BMD, hip BMD, BSAP, sCTX , ufDPD.	
Notes	Allocation of intervention - unclear. 46 of 78 consented participants completed the study.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not stated.

Chevrel 2006

Methods	Single center, double-blinded, placebo-controlled RCT. Parallel trial.	
Participants	64 adults (39 males) were randomized. Age range: >20 years (treatment: mean (SD) 37 (12); placebo mean (SD) 36 (12). All types of OI.	
Interventions	Oral alendronate versus placebo. Dosage: 10 mg. Study period: 36 months. Participants seen at baseline and during the 3 years of the study: every year in Lyon with intermediary visits at months 6, 18, and 30 by their local physician. BMD of the lumbar spine and of both hips (total femur) was measured at baseline and at 12, 24, and 36 months. Radiographs of the spine (anteroposterior and lateral views) were obtained at baseline and 36 months. Overall pain score was evaluated at baseline and every 6 months during 3 years with a visual analog scale score (0-10). Each participant underwent audiometry and impedancometry at baseline and at 36 months.	
Outcomes	Dietary calcium intake, spine BMD, hip BMD, spine radiographs, fractures, pain score, audiometry, impedancometry, serum and urine samples for biochemical markers of bone turnover, transiliac bone biopsies.	
Notes	Allocation intervention - adequate. Computer-generated list. Not adequately powered for fracture outcome.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	Adequate.

DiMeglio 2006

Methods	Single center, unblinded RCT. Parallel trial.
Participants	18 children (7 males) were randomized. Mean age: 8.7 years. Oral arm mean: 9 years (range 3.8 - 12.7 years); IV arm mean: 8.4 years (3 - 13.7 years). OI types I, III, IV included.
Interventions	Intravenous pamidronate disodium 1 mg/kg/day every 4 months compared to oral alendronate 1 mg/kg daily. Pamidronate diluted in 250 or 500 ml of normal saline given by slow infusion over 4 hours. Alendronate was given as 1 or 2 10 mg tablets, rounded to the nearest 10 mg dose for weight. Study period: 24 months. BMD, BMC, and area at the spine (L2-L4) and total body were measured every 4 months by DXA.
Outcomes	BMC, BMD, posteroanterior radiographs of left hand and wrist, radiographs of suspected fractures, blood and urine samples
Notes	Allocation of intervention - adequate. Computer random number generator.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Adequate.

Gatti 2005

Methods	Single center, unblinded, RCT. No placebo control. Parallel trial.
Participants	64 children 6 - 11 years were assigned to neridronate for 3 years (n = 44) or received no treatment for one year then received neridronate for two years (n = 22). All OI types included.
Interventions	Neridronate (2 mg/kg every 3 months) compared to no treatment. Study period: 36 months. After 12 months, the control group also received treatment (neridronate). All participants were seen at 3-monthly intervals, but full clinical evaluation, including bone densitometry measurements by DXA and fasting serum and urinary (second morning voiding) biochemistry, was obtained per-protocol every 6 months before the infusion of neridronate.
Outcomes	BMD and height/projected area of spine and total hip, fractures, markers of bone turnover.
Notes	Allocation of intervention - unclear.

Gatti 2005 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not stated.

Glorieux 2004

Methods	Multicenter, double-blinded, placebo-controlled RCT. Parallel trial.
Participants	139 children were randomized. Age range: 4 - 19 years. Not stated which type of OI, presumed all types.
Interventions	Oral alendronate versus placebo. Dosage: 5 - 10 mg/day for children <40 kg and 10 mg/day for children >40kg. Study period: 24 months.
Outcomes	spinal BMD z score, urinary NTx.
Notes	Not powered for fracture reduction.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not stated.

Letocha 2005

Methods	Single center, non blinded, RCT. No placebo control. Parallel trial.
Participants	18 children were randomized. Age range: 4 - 13 years. OI type III and IV included.
Interventions	IV pamidronate versus control. Dosage: 10 mg/m^2/day for 3 days every 3 months. Study period: 12 months initially, then 7 participants in the treatment group were given an additional 6 - 21 months of IV pamidronate. Note: 4 children in each group were receiving recombinant growth hormone (rGH) (0.06 mg/kg/day for 6 days/week).

Letocha 2005 (*Continued*)

	All participants were seen quarterly at the National Institutes of Health Clinical Center. Serum markers of bone formation and growth parameters were measured at each visit. Antero-posterior (AP) and lateral radiographs of the spine and lower extremity long bones and DXA at vertebrae L1-L4 were obtained at baseline and every 6 months. QCT scans of the spine were performed at the National Institutes of Health Clinical Center at 0 and 12 months.
Outcomes	L1 - L4 DXA, spine QCT, spine radiographs, musculoskeletal and functional testing.
Notes	Allocation of intervention - adequate. "Randomly-generated numbers".

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	Adequate.

Sakkers 2004

Methods	Single center, double-blinded, placebo-controlled RCT. Parallel trial.
Participants	34 children (16 male) were randomized. Age range: 3 to 18 years. OI types I, III and IV.
Interventions	Oral olpadronate versus placebo. Dosage: 10 mg/m^2 daily. Study period: 24 months.
Outcomes	Fractures, spinal BMC, spinal BMD, calcaneal BMC, calcaneal BMD, muscle strength, self care, mobility, height (body and seated), arm span, head circumference, body weight, heights of each lumbar vertebral body, urinary analysis, blood samples (but only 9 from each group). Adverse effects reported. BMC and BMD of the lumbar spine (L1 - L4) and of the os calcis were measured before randomisation, after 1 year, and at the end of the study. Domains of functional outcome were measured at the beginning of the study and every 6 months, and anthropometric and radiographic variables were measured every 12 months. All laboratory assessments were done at baseline and at 3 months, 12 months, and 24 months.
Notes	Allocation of intervention by computer-generated randomization.

Risk of bias

Item	**Authors' judgement**	**Description**

Sakkers 2004 (*Continued*)

Allocation concealment?	Yes	Adequate; researchers "were not aware of treatment allocation".

Seikaly 2005

Methods	Single center, double-blinded, placebo-controlled RCT. Cross-over trial.
Participants	20 children (11 males) were randomized. 17 completed. Age range: 3 - 15 years. Mean (SD) 9.8 (1.06) years; median 10.53 years. OI types: I, III, IV.
Interventions	Oral alendronate versus placebo. Dosage: 5 mg/d (participants who weighed <30 kg); or 10 mg/d (participants who weighed >30kg). Study period: 24 months (12 months each study period). Participants were evaluated at baseline, every 3 months thereafter (except when otherwise indicated), and at the conclusion of the study.
Outcomes	Physical evaluation, food records, blood and urine analysis, stool guaiac, DEXA, renal ultrasound, skeletal survey.
Notes	Allocation of intervention - adequate. Computer-generated randomization.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	Adequate.

BMC: bone mineral content
BMD: bone mineral density
BSAP: bone-specific alkaline phosphatase
DEXA, DXA: dual-energy x-ray absorptiometry
IV: intravenous
NTx: N-linked telopeptides
OI: osteogenesis imperfecta
QCT:quantitative computer-assisted tomography
RCT: randomized controlled trial
sCTX: serum cross-laps
SD: standard deviation
ufDPD: urinary free-deoxy pyridinoline
vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Antoniazzi 1996	Not a randomized controlled trial.
Antoniazzi 2006	Not a randomized controlled trial.
DiMeglio 2004	Not a randomized controlled trial.
Gerber 1998	Not a bisphosphonate therapy - leg braces.
Granda 1977	Evaluated pyrophosphate levels in OI disease severity not improved in bone density or fracture reduction.
Ward 2005	Not a randomized controlled trial. An open label, oral bioavailability study. Does not address the outcomes of interest.

OI: osteogenesis imperfecta

Characteristics of ongoing studies *[ordered by study ID]*

Teriparatide 2008

Trial name or title	A study to assess the effectiveness of teriparatide (FORTEO) for increasing bone mass and improving bone structure in adults affected with OI. Study ID numbers: IBMD-OI. ClinicalTrials.gov identifier NCT00063479.
Methods	Randomized (phase IV), double-blinded, placebo-controlled cross-over study. 3 clinic sites: Oregon Health & Science University (Portland); Kennedy Krieger Institute (Johns Hopkins University, Baltimore); and Baylor College of Medicine (Houston).
Participants	Adults 18 - 85 years, male and female. Total enrolment: 90. Eligibility criteria: previous established diagnosis of OI AND > 2 previous adult fractures, AND/OR BMD at lumbar spine, femoral neck or total hip T score < -2.0.
Interventions	Teriparatide 20 mcg sub-q. Participants to be enrolled for approximately 18 months.
Outcomes	Spine and hip BMD, fractures. Blood, urine, and bone density tests will be done during the study for safety monitoring and to see if the PTH is working.
Starting date	05/03/2005.

Teriparatide 2008 (*Continued*)

Contact information	Jan Reeder (reederjan@cebridge.net). Sandra Veith (veithsa@ohsu.edu).
Notes	Multicenter Study. Investigator Initiated Trial. Financial assistance: Eli Lilly Co, NIH, OIF

Zoledronic Acid 2008

Trial name or title	Bisphosphonate treatment of OI. Study ID numbers: CZOL446H2202. ClinicalTrials.gov identifier NCT00063479.
Methods	Randomized (Phase II), open label, active control, parallel assignment, safety/efficacy study. 9 clinic sites: UCLA (Los Angeles, USA); Alfred I. DuPont Hospital for Children (Delaware, USA); Intermountain Orthopedics (Idaho, USA); St Jude Children's Research Hospital (Illinois, USA); Children's Hospital (Nebraska, USA); Children's Hospital Medical Center (Ohio, USA); Oregon Health & Science University (Portland, USA); Vanderbilt University Medical Center (Tennessee, USA); Texas Chilren's Hospital (Texas, USA).
Participants	Children 3 months - 17 years, male and female. Estimated total enrolment: 158. Eligibility criteria: OI type I, III or IV.
Interventions	Zoledronic acid.
Outcomes	Primary outcome measure: change in lumbar spine BMD at month 12 relative to baseline. Secondary outcome measure: Change in z score of the lumbar spine at month 12 relative to baseline.
Starting date	June 2003.
Contact information	
Notes	Multicenter Study. Financial assistance: Novartis.

BMD: bone mineral density
mcg: microgram
OI: osteogenesis imperfecta
sub-q: subcutaneously
PTH: parathormone

DATA AND ANALYSES

Comparison 1. Oral bisphosphonates versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fracture risk reduction	1		Hazard ratio (Fixed, 95% CI)	Totals not selected
1.1 2 year follow-up	1		Hazard ratio (Fixed, 95% CI)	Not estimable
2 Number of fractures	1		Relative rate (Fixed, 95% CI)	Totals not selected
3 Number of people with at least one fracture	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Mean change (z score) in spine BMD (DEXA)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Mean % change in spine BMD (DEXA)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 12 months	1		Mean Difference (IV, Random, 95% CI)	Not estimable
5.2 24 months	1		Mean Difference (IV, Random, 95% CI)	Not estimable
5.3 36 months	1		Mean Difference (IV, Random, 95% CI)	Not estimable
6 Mean % change in total femur BMD (DEXA)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 At 36 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
7 Change in height	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 At 12 month (z score)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Change in bone pain scores	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	-3.64 [-5.17, -2.09]
8.2 At 36 months	1		Mean Difference (IV, Fixed, 95% CI)	1.04 [0.14, 2.46]
9 Change in analgesic use (days per week)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 Change in well-being score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Change in self-care score (PEDI)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Change in total mobility score (WeeFIM)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13 Hearing (assessed by % rinnie)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. IV bisphosphonates versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with at least one fracture	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 At 1 year	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.30, 1.06]
2 Incidence of lower extremity fractures	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

2.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Incidence of upper extremity fractures	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Mean % change (from baseline) in spine BMD (DEXA)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 At 6 months	2	125	Mean Difference (IV, Random, 95% CI)	9.96 [-2.51, 22.43]
4.2 At 12 months	2	125	Mean Difference (IV, Random, 95% CI)	14.68 [-6.08, 35.45]
5 Mean % change (z score) in spine BMD (DEXA)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.2 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Mean % change in total hip BMD (DEXA)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 06 months	2	108	Mean Difference (IV, Random, 95% CI)	6.16 [-3.57, 15.90]
6.2 12 months	2	108	Mean Difference (IV, Random, 95% CI)	11.27 [-3.69, 26.22]
7 Change in growth	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 At 12 months (cm/year)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Bone pain scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
9 Muscle strength	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
10 BAMF (10-point gross motor assessment)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 3. Oral versus IV bisphosphonates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Annualised fracture rates	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Spine BMD z scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.30 [-1.11, 1.71]
2.2 At 24 months	1		Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.32, 1.72]
3 Change in alkaline phosphonate (IU/liter)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 At 4 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Change in bone alkaline phosphatase (IU/liter)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 At 4 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Change in NTX/Cr (nMBCE/mM)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 At 4 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.2 At 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Oral bisphosphonates versus placebo, Outcome 1 Fracture risk reduction.

Review: Bisphosphonate therapy for osteogenesis imperfecta

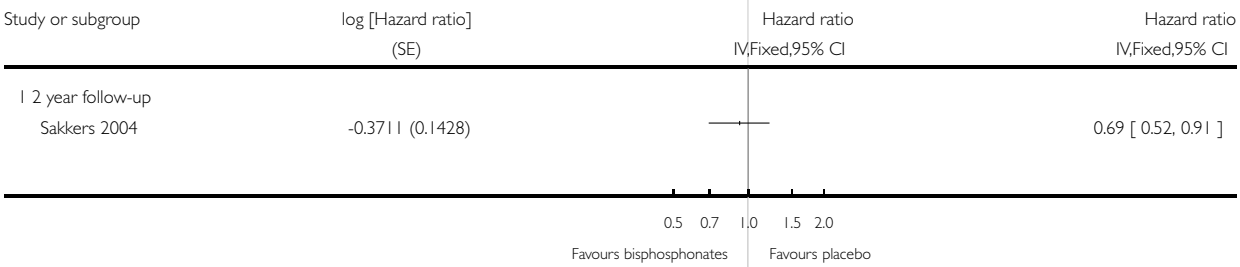
Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 1 Fracture risk reduction

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 1 Fracture risk reduction



Analysis 1.2. Comparison 1 Oral bisphosphonates versus placebo, Outcome 2 Number of fractures.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

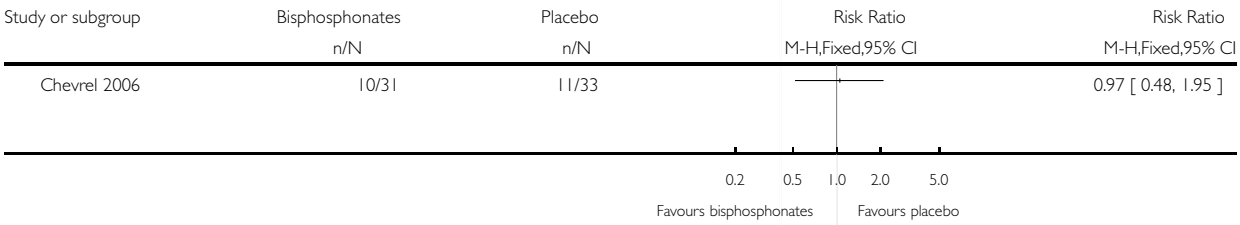
Outcome: 2 Number of fractures

Analysis 1.3. Comparison 1 Oral bisphosphonates versus placebo, Outcome 3 Number of people with at least one fracture.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 3 Number of people with at least one fracture



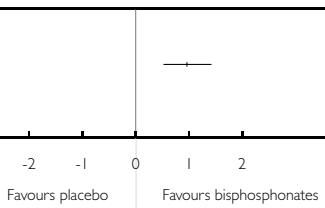
Analysis 1.4. Comparison 1 Oral bisphosphonates versus placebo, Outcome 4 Mean change (z score) in spine BMD (DEXA).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 4 Mean change (z score) in spine BMD (DEXA)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Seikaly 2005	20	0.89 (0.85)	20	-0.12 (0.63)		1.01 [0.55, 1.47]



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 4 Mean change (z score) in spine BMD (DEXA)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Seikaly 2005	20	0.89 (0.85)	20	-0.12 (0.63)		1.01 [0.55, 1.47]

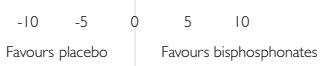
Analysis 1.5. Comparison 1 Oral bisphosphonates versus placebo, Outcome 5 Mean % change in spine BMD (DEXA).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 5 Mean % change in spine BMD (DEXA)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 12 months						
Chevrel 2006	31	7.5 (8)	33	0.5 (4)		7.00 [3.87, 10.13]
2 24 months						
Chevrel 2006	31	9 (8.5)	33	0.2 (6)		8.80 [5.17, 12.43]
3 36 months						
Chevrel 2006	31	10.1 (9.8)	33	0.7 (5.7)		9.40 [5.44, 13.36]



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 5 Mean % change in spine BMD (DEXA)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 12 months						
Chevrel 2006	31	7.5 (8)	33	0.5 (4)		7.00 [3.87, 10.13]

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 5 Mean % change in spine BMD (DEXA)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
2 24 months						
Chevrel 2006	31	9 (8.5)	33	0.2 (6)		8.80 [5.17, 12.43]

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 5 Mean % change in spine BMD (DEXA)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
3 36 months						
Chevrel 2006	31	10.1 (9.8)	33	0.7 (5.7)		9.40 [5.44, 13.36]

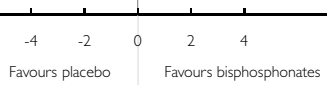
Analysis 1.6. Comparison 1 Oral bisphosphonates versus placebo, Outcome 6 Mean % change in total femur BMD (DEXA).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 6 Mean % change in total femur BMD (DEXA)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 36 months						
Chevrel 2006	31	3.3 (0.5)	33	0.3 (0.6)		3.00 [2.73, 3.27]



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 6 Mean % change in total femur BMD (DEXA)

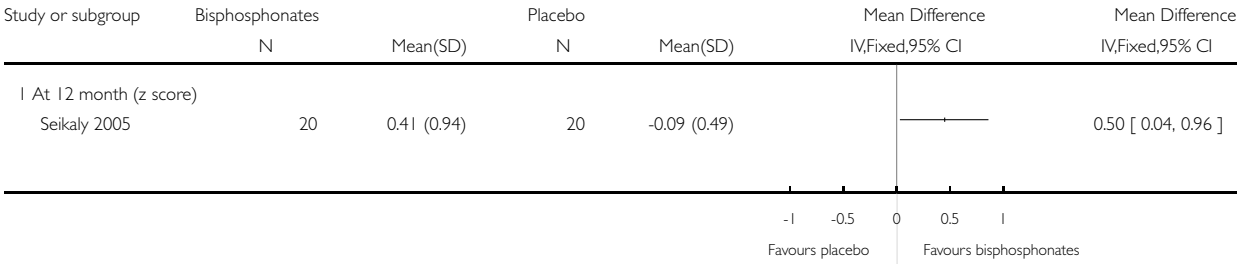
Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 36 months						
Chevrel 2006	31	3.3 (0.5)	33	0.3 (0.6)		3.00 [2.73, 3.27]

Analysis 1.7. Comparison 1 Oral bisphosphonates versus placebo, Outcome 7 Change in height.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

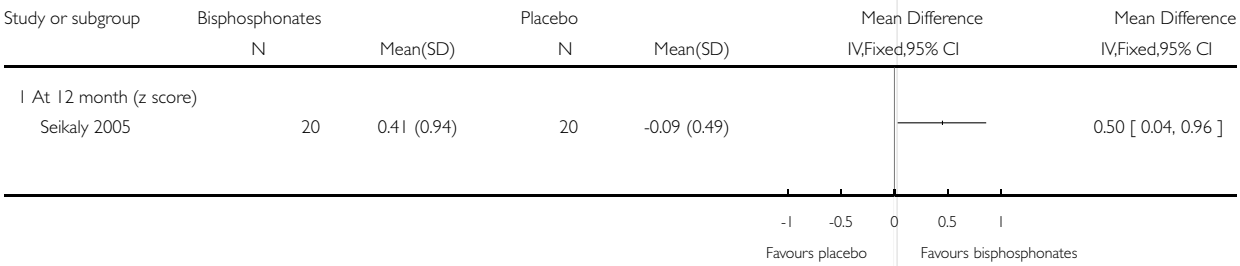
Outcome: 7 Change in height



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 7 Change in height

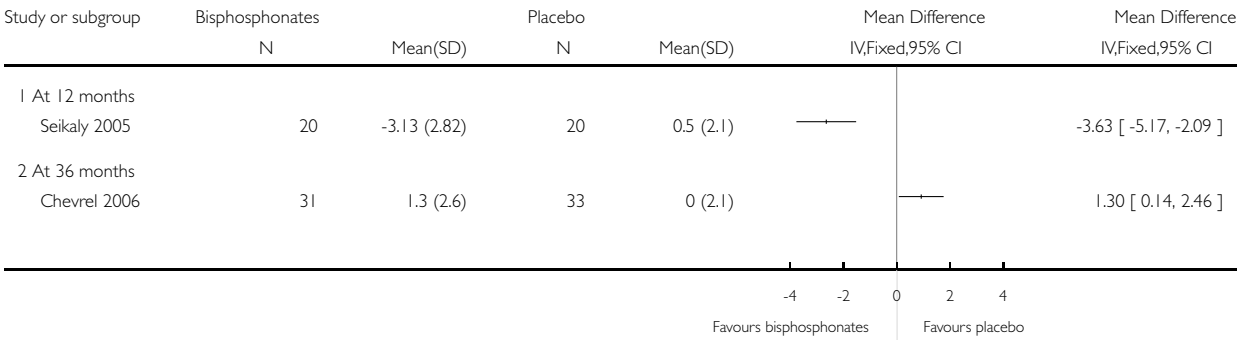


Analysis 1.8. Comparison 1 Oral bisphosphonates versus placebo, Outcome 8 Change in bone pain scores.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

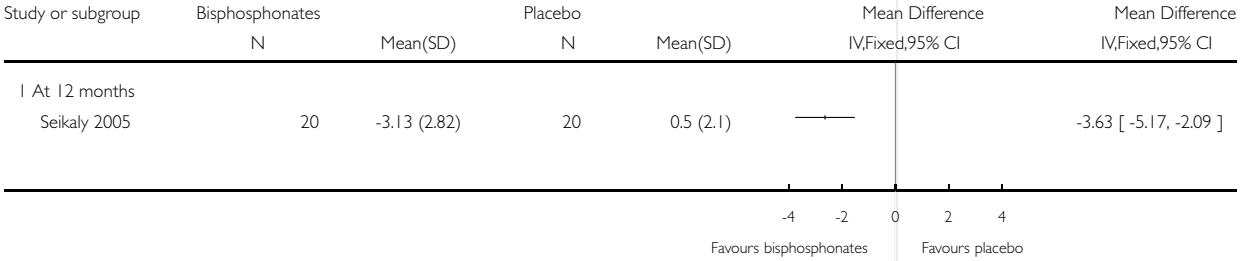
Outcome: 8 Change in bone pain scores



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 8 Change in bone pain scores

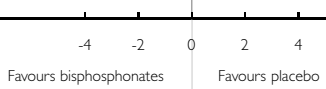


Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 8 Change in bone pain scores

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
2 At 36 months						
Chevrel 2006	31	1.3 (2.6)	33	0 (2.1)		1.30 [0.14, 2.46]



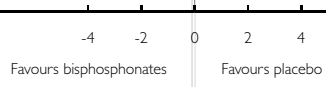
Analysis 1.9. Comparison 1 Oral bisphosphonates versus placebo, Outcome 9 Change in analgesic use (days per week).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 9 Change in analgesic use (days per week)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Seikaly 2005	20	-1.44 (2.91)	20	0.56 (2.1)		-2.00 [-3.57, -0.43]



Analysis 1.10. Comparison 1 Oral bisphosphonates versus placebo, Outcome 10 Change in well-being score.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 10 Change in well-being score

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Seikaly 2005	20	3.25 (1.83)	20	0.06 (1.12)		3.19 [2.25, 4.13]

Analysis 1.11. Comparison 1 Oral bisphosphonates versus placebo, Outcome 11 Change in self-care score (PEDI).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 11 Change in self-care score (PEDI)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Seikaly 2005	20	3.82 (2.28)	20	0.24 (5.28)		3.58 [1.06, 6.10]

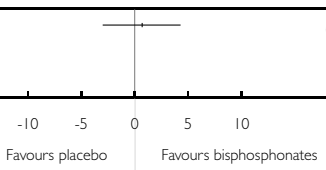
Analysis 1.12. Comparison 1 Oral bisphosphonates versus placebo, Outcome 12 Change in total mobility score (WeeFIM).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 12 Change in total mobility score (WeeFIM)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Seikaly 2005	20	3 (8.23)	20	2.21 (4.47)		0.79 [-3.31, 4.89]



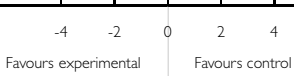
Analysis 1.13. Comparison 1 Oral bisphosphonates versus placebo, Outcome 13 Hearing (assessed by % rinnie).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 1 Oral bisphosphonates versus placebo

Outcome: 13 Hearing (assessed by % rinnie)

Study or subgroup	Bisphosphonates N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Chevrel 2006	31	-1 (6.3)	33	-0.9 (4.9)		-0.10 [-2.88, 2.68]

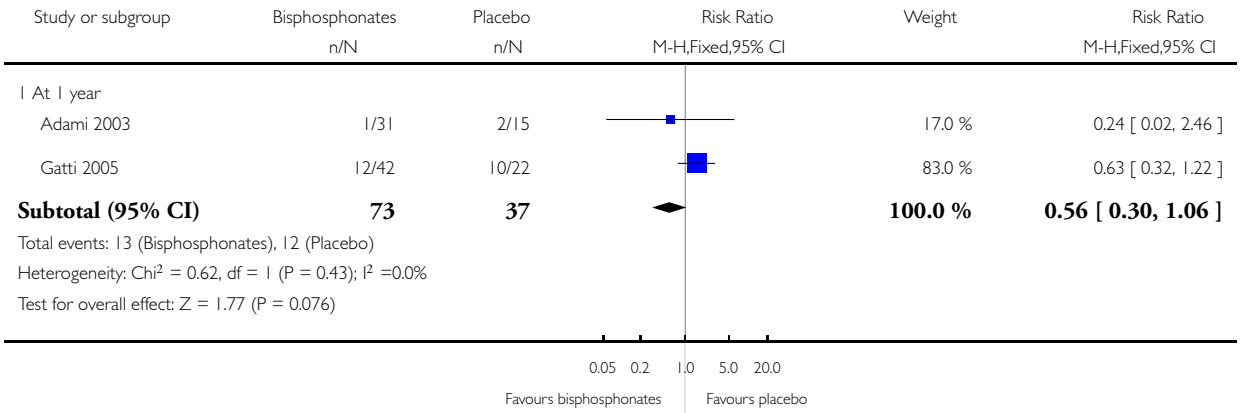


Analysis 2.1. Comparison 2 IV bisphosphonates versus placebo or no treatment, Outcome 1 Number of participants with at least one fracture.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

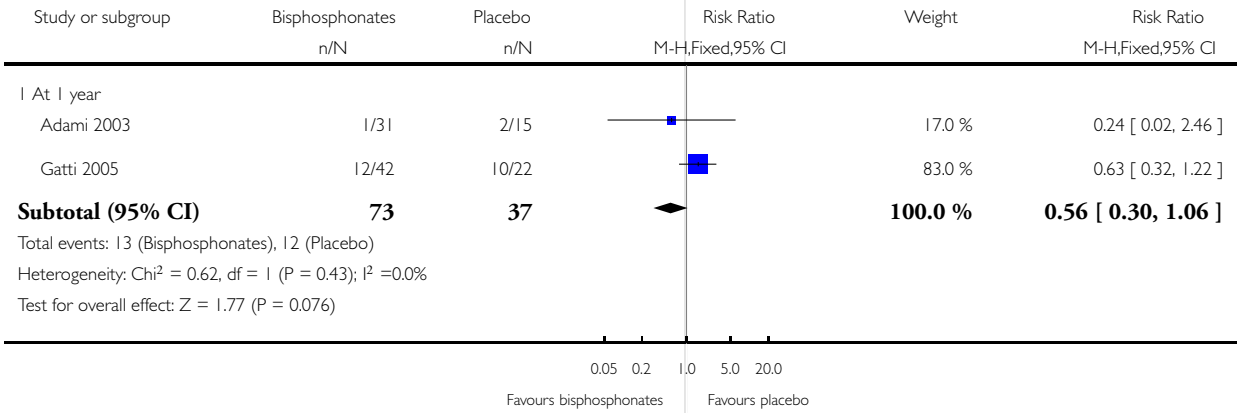
Outcome: 1 Number of participants with at least one fracture



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 1 Number of participants with at least one fracture



Analysis 2.2. Comparison 2 IV bisphosphonates versus placebo or no treatment, Outcome 2 Incidence of lower extremity fractures.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 2 Incidence of lower extremity fractures

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Letocha 2005	9	0.67 (0.87)	9	0.78 (0.97)		-0.11 [-0.96, 0.74]

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 2 Incidence of lower extremity fractures

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Letocha 2005	9	0.67 (0.87)	9	0.78 (0.97)		-0.11 [-0.96, 0.74]

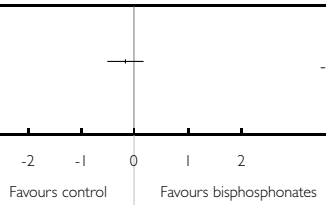
Analysis 2.3. Comparison 2 IV bisphosphonates versus placebo or no treatment, Outcome 3 Incidence of upper extremity fractures.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 3 Incidence of upper extremity fractures

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Letocha 2005	9	0.22 (0.44)	9	0.44 (0.53)		-0.22 [-0.67, 0.23]

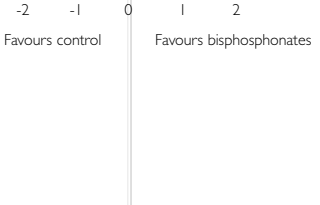


Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 3 Incidence of upper extremity fractures

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Letocha 2005	9	0.22 (0.44)	9	0.44 (0.53)		-0.22 [-0.67, 0.23]



Analysis 2.4. Comparison 2 IV bisphosphonates versus placebo or no treatment, Outcome 4 Mean % change (from baseline) in spine BMD (DEXA).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 4 Mean % change (from baseline) in spine BMD (DEXA)

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 At 6 months							
Adami 2003	46	3 (6.4)	15	-0.8 (9.1)		51.6 %	3.80 [-1.16, 8.76]
Gatti 2005	42	18.03 (12.44)	22	1.5 (13.14)		48.4 %	16.53 [9.87, 23.19]
Subtotal (95% CI)	**88**		**37**			**100.0 %**	**9.96 [-2.51, 22.43]**
Heterogeneity: Tau^2 = 72.05; Chi^2 = 9.03, df = 1 (P = 0.003); I^2 =89%							
Test for overall effect: Z = 1.57 (P = 0.12)							
2 At 12 months							
Adami 2003	46	3.6 (5.4)	15	-0.8 (7.7)		54.0 %	4.40 [0.20, 8.60]
Gatti 2005	42	29 (18.54)	22	3.4 (14.73)		46.0 %	25.60 [17.27, 33.93]
Subtotal (95% CI)	**88**		**37**			**100.0 %**	**14.68 [-6.08, 35.45]**
Heterogeneity: Tau^2 = 213.40; Chi^2 = 19.86, df = 1 (P<0.00001); I^2 =95%							
Test for overall effect: Z = 1.39 (P = 0.17)							

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 4 Mean % change (from baseline) in spine BMD (DEXA)

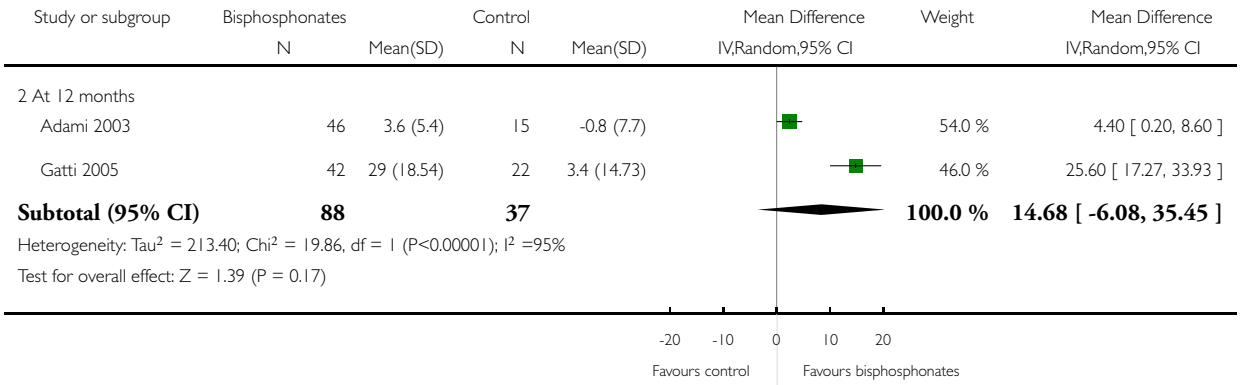
Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 At 6 months							
Adami 2003	46	3 (6.4)	15	-0.8 (9.1)		51.6 %	3.80 [-1.16, 8.76]
Gatti 2005	42	18.03 (12.44)	22	1.5 (13.14)		48.4 %	16.53 [9.87, 23.19]
Subtotal (95% CI)	**88**		**37**			**100.0 %**	**9.96 [-2.51, 22.43]**
Heterogeneity: Tau^2 = 72.05; Chi^2 = 9.03, df = 1 (P = 0.003); I^2 =89%							
Test for overall effect: Z = 1.57 (P = 0.12)							

-20 -10 0 10 20
Favours control Favours bisphosphonates

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 4 Mean % change (from baseline) in spine BMD (DEXA)

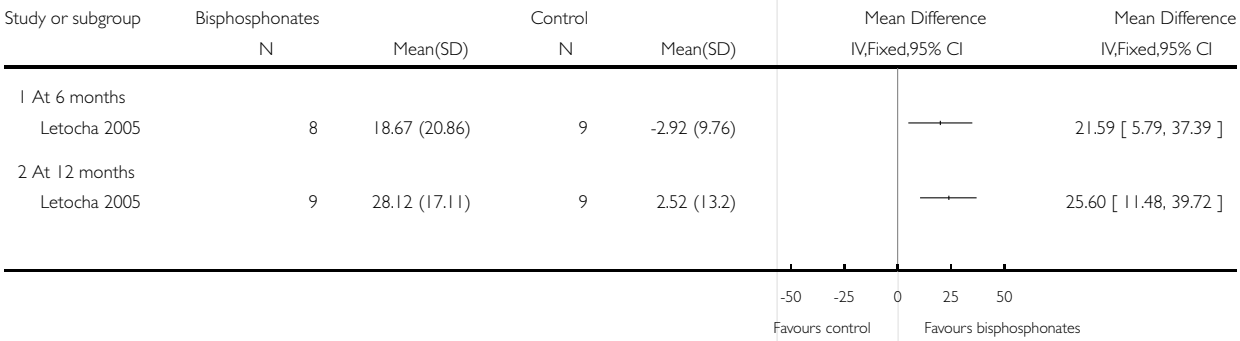


Analysis 2.5. Comparison 2 IV bisphosphonates versus placebo or no treatment, Outcome 5 Mean % change (z score) in spine BMD (DEXA).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

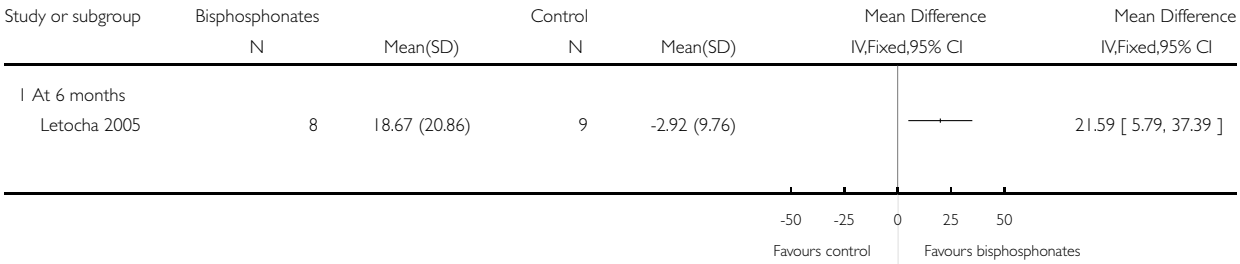
Outcome: 5 Mean % change (z score) in spine BMD (DEXA)



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

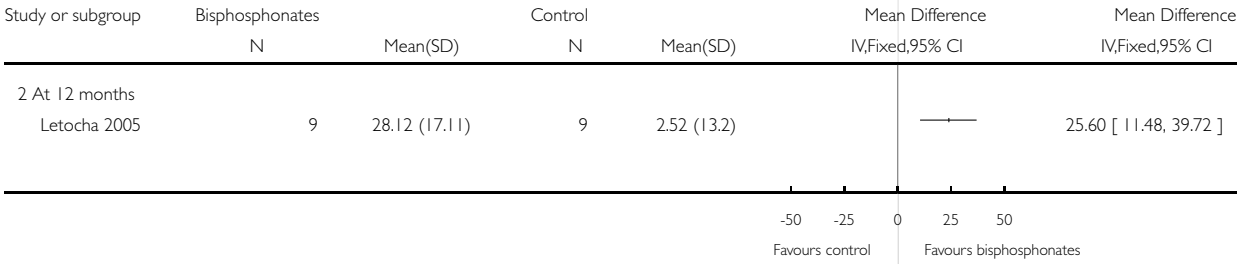
Outcome: 5 Mean % change (z score) in spine BMD (DEXA)



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 5 Mean % change (z score) in spine BMD (DEXA)



Analysis 2.6. Comparison 2 IV bisphosphonates versus placebo or no treatment, Outcome 6 Mean % change in total hip BMD (DEXA).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 6 Mean % change in total hip BMD (DEXA)

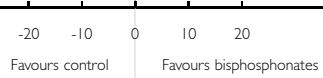
Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 06 months							
Adami 2003	29	1.2 (3.5)	15	-0.2 (4.1)		52.8 %	1.40 [-1.03, 3.83]
Gatti 2005	42	13.24 (8.8)	22	1.9 (9.12)		47.2 %	11.34 [6.69, 15.99]
Subtotal (95% CI)	**71**		**37**			**100.0 %**	**6.16 [-3.57, 15.90]**
Heterogeneity: Tau² = 45.82; Chi² = 13.78, df = 1 (P = 0.00020); I² =93%							
Test for overall effect: Z = 1.24 (P = 0.21)							
2 12 months							
Adami 2003	29	3.5 (3.9)	15	-0.5 (5.2)		57.1 %	4.00 [1.01, 6.99]
Gatti 2005	42	24.98 (17.2)	22	5.7 (12.18)		42.9 %	19.28 [12.00, 26.56]
Subtotal (95% CI)	**71**		**37**			**100.0 %**	**11.27 [-3.69, 26.22]**
Heterogeneity: Tau² = 108.68; Chi² = 14.49, df = 1 (P = 0.00014); I² =93%							
Test for overall effect: Z = 1.48 (P = 0.14)							

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 6 Mean % change in total hip BMD (DEXA)

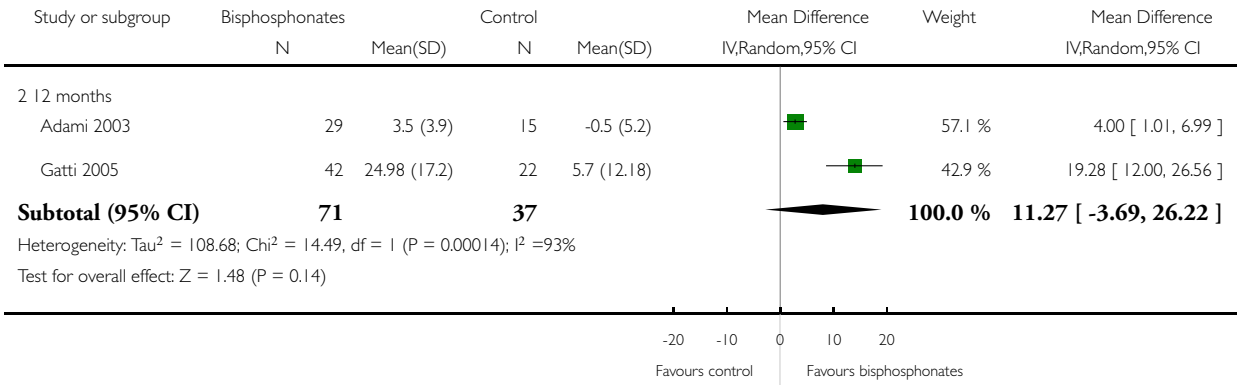
Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 06 months							
Adami 2003	29	1.2 (3.5)	15	-0.2 (4.1)		52.8 %	1.40 [-1.03, 3.83]
Gatti 2005	42	13.24 (8.8)	22	1.9 (9.12)		47.2 %	11.34 [6.69, 15.99]
Subtotal (95% CI)	**71**		**37**			**100.0 %**	**6.16 [-3.57, 15.90]**
Heterogeneity: Tau² = 45.82; Chi² = 13.78, df = 1 (P = 0.00020); I² =93%							
Test for overall effect: Z = 1.24 (P = 0.21)							



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 6 Mean % change in total hip BMD (DEXA)

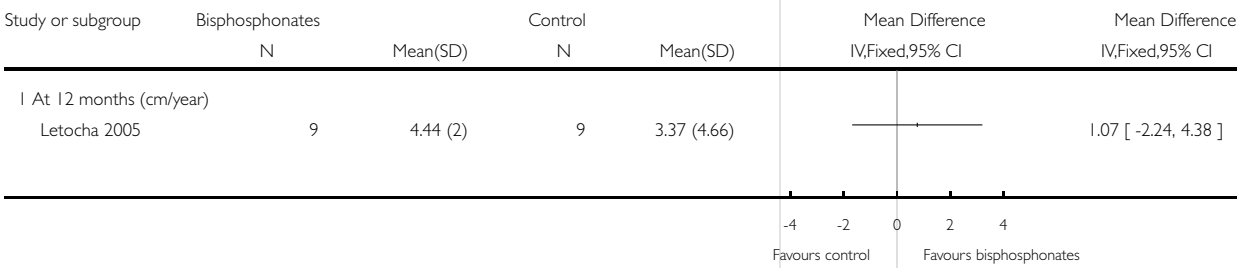


Analysis 2.7. Comparison 2 IV bisphosphonates versus placebo or no treatment, Outcome 7 Change in growth.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 7 Change in growth



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 7 Change in growth

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months (cm/year)						
Letocha 2005	9	4.44 (2)	9	3.37 (4.66)		1.07 [-2.24, 4.38]

Analysis 2.8. Comparison 2 IV bisphosphonates versus placebo or no treatment, Outcome 8 Bone pain scores.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 8 Bone pain scores

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Letocha 2005	9	3.44 (0.82)	9	3.55 (0.73)		-0.11 [-0.83, 0.61]

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 8 Bone pain scores

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Letocha 2005	9	3.44 (0.82)	9	3.55 (0.73)		-0.11 [-0.83, 0.61]

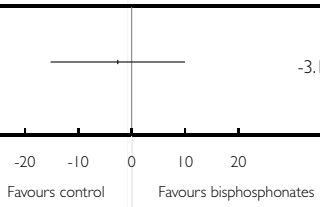
Analysis 2.9. Comparison 2 IV bisphosphonates versus placebo or no treatment, Outcome 9 Muscle strength.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 9 Muscle strength

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Letocha 2005	9	71.42 (19.48)	9	74.6 (14.3)		-3.18 [-18.97, 12.61]

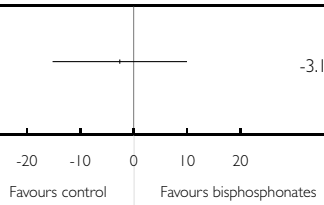


Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 9 Muscle strength

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Letocha 2005	9	71.42 (19.48)	9	74.6 (14.3)		-3.18 [-18.97, 12.61]



Analysis 2.10. Comparison 2 IV bisphosphonates versus placebo or no treatment, Outcome 10 BAMF (10-point gross motor assessment).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 10 BAMF (10-point gross motor assessment)

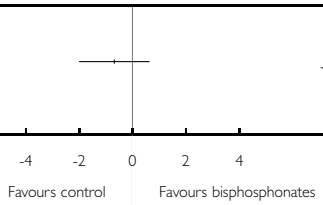
Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Letocha 2005	9	6.22 (2.11)	9	7.02 (1.31)		-0.80 [-2.42, 0.82]

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 2 IV bisphosphonates versus placebo or no treatment

Outcome: 10 BAMF (10-point gross motor assessment)

Study or subgroup	Bisphosphonates N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 12 months						
Letocha 2005	9	6.22 (2.11)	9	7.02 (1.31)		-0.80 [-2.42, 0.82]



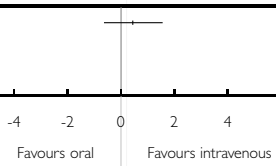
Analysis 3.1. Comparison 3 Oral versus IV bisphosphonates, Outcome 1 Annualised fracture rates.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 1 Annualised fracture rates

Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
DiMeglio 2006	9	1.4 (1.5)	9	0.9 (0.9)		0.50 [-0.64, 1.64]

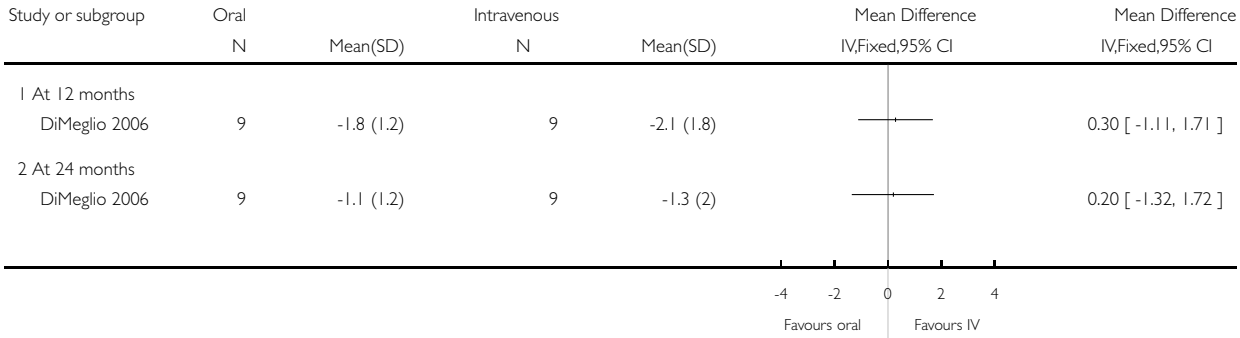


Analysis 3.2. Comparison 3 Oral versus IV bisphosphonates, Outcome 2 Spine BMD z scores.

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

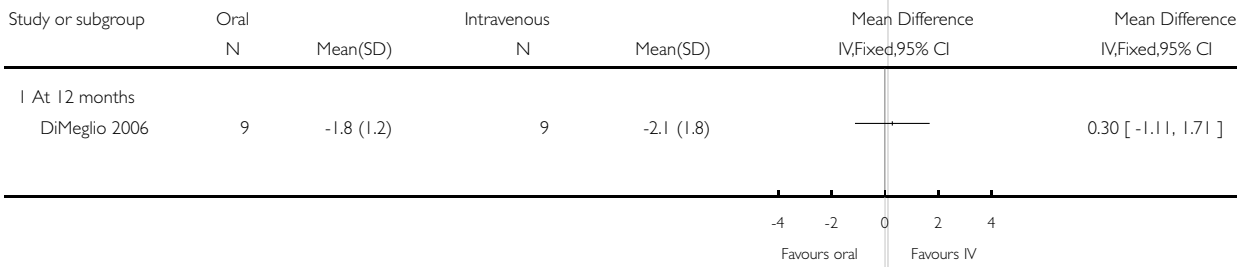
Outcome: 2 Spine BMD z scores



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 2 Spine BMD z scores

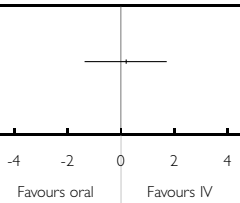


Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 2 Spine BMD z scores

Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
2 At 24 months						
DiMeglio 2006	9	-1.1 (1.2)	9	-1.3 (2)		0.20 [-1.32, 1.72]



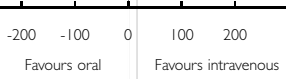
Analysis 3.3. Comparison 3 Oral versus IV bisphosphonates, Outcome 3 Change in alkaline phosphonate (IU/liter).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 3 Change in alkaline phosphonate (IU/liter)

Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 4 months						
DiMeglio 2006	9	237 (90)	9	249 (69)		-12.00 [-86.09, 62.09]
2 At 12 months						
DiMeglio 2006	9	209 (73)	9	244 (99)		-35.00 [-115.36, 45.36]



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 3 Change in alkaline phosphonate (IU/liter)

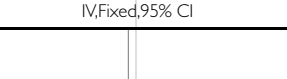
Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 4 months						
DiMeglio 2006	9	237 (90)	9	249 (69)		-12.00 [-86.09, 62.09]

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 3 Change in alkaline phosphonate (IU/liter)

Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
2 At 12 months						
DiMeglio 2006	9	209 (73)	9	244 (99)		-35.00 [-115.36, 45.36]



Analysis 3.4. Comparison 3 Oral versus IV bisphosphonates, Outcome 4 Change in bone alkaline phosphatase (IU/liter).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 4 Change in bone alkaline phosphatase (IU/liter)

Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 4 months						
DiMeglio 2006	9	76 (35)	9	71 (23)		5.00 [-22.36, 32.36]
2 At 12 months						
DiMeglio 2006	9	66 (28)	9	78 (32)		-12.00 [-39.78, 15.78]

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 4 Change in bone alkaline phosphatase (IU/liter)

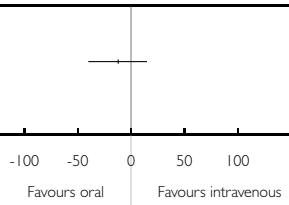
Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 4 months						
DiMeglio 2006	9	76 (35)	9	71 (23)		5.00 [-22.36, 32.36]

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 4 Change in bone alkaline phosphatase (IU/liter)

Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
2 At 12 months						
DiMeglio 2006	9	66 (28)	9	78 (32)		-12.00 [-39.78, 15.78]



Analysis 3.5. Comparison 3 Oral versus IV bisphosphonates, Outcome 5 Change in NTX/Cr (nMBCE/mM).

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 5 Change in NTX/Cr (nMBCE/mM)

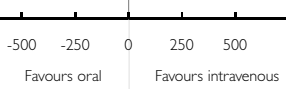
Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 4 months						
DiMeglio 2006	9	366 (216)	9	474 (200)		-108.00 [-300.32, 84.32]
2 At 12 months						
DiMeglio 2006	9	240 (200)	9	351 (137)		-111.00 [-269.38, 47.38]

Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 5 Change in NTX/Cr (nMBCE/mM)

Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 4 months						
DiMeglio 2006	9	366 (216)	9	474 (200)		-108.00 [-300.32, 84.32]



Review: Bisphosphonate therapy for osteogenesis imperfecta

Comparison: 3 Oral versus IV bisphosphonates

Outcome: 5 Change in NTX/Cr (nMBCE/mM)

Study or subgroup	Oral N	Mean(SD)	Intravenous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
2 At 12 months						
DiMeglio 2006	9	240 (200)	9	351 (137)		-111.00 [-269.38, 47.38]

WHAT'S NEW

Last assessed as up-to-date: 5 August 2008.

28 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 4, 2008

CONTRIBUTIONS OF AUTHORS

Robert Steiner (RS) conceived the review.

RS and Janet Reeder wrote the protocol.

Carrie Phillipi (CP) and RS independently examined and evaluated all relevant studies and drafted the text, with input from Tracey Remmington (TR).

CP and TR input the data into the review.

CP acts as guarantor of the review.

DECLARATIONS OF INTEREST

Dr Steiner has participated in clinical trials of pharmacologic agents for OI sponsored by Shriners Hospitals, Merck, Novartis, and Aventis/Proctor and Gamble. Dr Steiner is a co-investigator with Janet Reeder (lead author on the protocol only) on an investigator-initiated study of treatment for adults with OI which is financially supported by Eli Lilly, the Osteogenesis Imperfecta Foundation and the National Institutes of Health.

Janet Reeder has been a guest lecturer for Aventis Pharmaceuticals, Inc.

Dr Phillipi and Ms Remmington report no potential conflicts.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Title change from 'Pharmacologic therapy for osteogenesis imperfecta' to more accurately refect the content of the review.