ORIGINAL ARTICLE

Systematic review of effectiveness of bisphosphonates in treatment of low bone mineral density and fragility fractures in juvenile idiopathic arthritis

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Arch Dis Child 2006;91:753–761. doi: 10.1136/adc.2006.093997

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Accepted 26 April 2006
Published Online First
11 May 2006

Aims: To evaluate the currently available evidence for the effectiveness of bisphosphonates in children with low bone mineral density (BMD) and fragility fractures associated with juvenile idiopathic arthritis (JIA), and the safety of bisphosphonates in JIA and other conditions.

Methods: Literature databases were searched using a structured search strategy. The effectiveness review included any studies of children with JIA treated with bisphosphonates. The safety review also included studies of osteogenesis imperfecta. Quantitative data analysis was not undertaken because of the heterogeneity of the studies; findings were summarised using tables and narrative synthesis.

Results: Ninety four studies were identified. Sixteen studies (78 JIA children) were included in the effectiveness review: one randomised controlled trial, three controlled cohort studies, 11 case series, and one case report. At baseline, children had low BMD below the expected values for age and sex matched children. In all studies, treatment with bisphosphonates increased BMD compared with baseline: the mean percentage increase in spine BMD ranged from 4.5% to 19.1%. Overall, studies were heterogeneous and of variable quality. A total of 59 papers were included in the safety review; treatment durations were up to three years. The most common side effect was a flu-like reaction with intravenous treatment. This occurred during the first infusion and was transient; the symptoms were managed with paracetamol and did not occur during subsequent cycles.

Conclusions: Bisphosphonates are a promising treatment for low BMD and fragility fractures in children with JIA. However, the quality of the current evidence is variable and better studies are needed to more clearly assess their role.

Fragility fractures are well recognised serious long term complications of juvenile idiopathic arthritis (JIA) and are associated with considerable morbidity and impaired quality of life. In a study using the UK General Practice Research Database, there was a statistically significantly greater number of fractures in subjects with childhood onset arthritis compared with healthy controls.¹ Adults with a history of JIA have reduced bone mineral density and increased bone turnover compared with healthy control subjects.^{2–3}

Bone mineral content (BMC) and bone mineral density (BMD), which are the quantifiable parameters of bone strength in vivo, account for approximately 60% of the total bone strength or the resistance to fracture.⁴ Dual energy x ray absorptiometry (DXA) is the most commonly used technique for measurement of BMC and BMD in children and adults. DXA calculates density from the scanned area of bone and estimates areal BMD (aBMD) as g/cm². In postmenopausal Caucasian women, the World Health Organization arbitrarily defined osteopenia as those with an aBMD between more than 1 standard deviation (SD) but less than 2.5 SD and osteoporosis as aBMD of more than 2.5 SD below the mean for young adult women.⁵ In adults, the risk of fracture appears to double for each 1 SD decrease in BMD.⁶ There is no clear definition of osteopenia or osteoporosis in children. However, in girls with a previous forearm fracture, Goulding *et al* observed that for every 1 SD decrease of total body BMD the risk of new fractures at any site doubled during the four years after initial fracture,⁷ thus supporting the concept that low BMD is the major contributing factor to skeletal fragility.

Known risk factors for low BMD and fragility fractures in children with JIA include the inflammatory process,⁸ nutrition,⁹ growth impairment,¹⁰ reduced physical activity,⁹ and treatment, especially corticosteroids.^{11–12} The risk of osteoporosis can be reduced by ensuring good nutrition,¹³ encouraging weight bearing exercise,¹⁴ and supplementation with calcium and vitamin D.¹⁴ In adults, bisphosphonates are an effective treatment for osteoporosis, with studies showing improvements in BMD at the spine and hip and a reduction in fracture risk,¹⁵ but there is much less information about their use in children. A recent review of bisphosphonate treatment in children's bone disease showed the potential of these agents,¹⁶ but there are long term safety concerns about giving these agents to children,¹⁶ particularly with regard to the growing skeleton.¹⁷ The aim of this systematic review was to evaluate the currently available evidence for the effectiveness and safety of bisphosphonates, specifically in children with JIA.

METHODS

Identification of studies

We searched Medline (Ovid 1966 to 2005), Embase (Ovid 1980 to 2005), Cochrane Library, ISI Web of Science (1981 to 2005), and Current Controlled Trials using structured electronic search strategies in the format: ("bisphosphonate")

Abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; DXA, dual energy x ray absorptiometry; JIA, juvenile idiopathic arthritis

combined with ("osteoporosis" or "bone mineral density") and ("children"). We checked bibliographies of identified papers for further studies. For the effectiveness review, all studies (full papers and conference abstracts) including children with JIA or other connective tissue disease treated with bisphosphonates were included. To increase the number of children in the safety review, studies in osteogenesis imperfecta were also included.

Quality assessment and extraction of data

Data extraction and quality assessment forms, that would be suitable for subjective assessment of all types of studies, were developed by the authors for use in this review. As well as methodology and results, issues of bias relevant to a range of study types were addressed (selection, performance, attrition, and detection biases).¹⁸ The outcomes of treatment included bone status assessed with densitometry using DXA or other methods; aBMD is calculated by dividing BMC by the scanned area but, based on assumptions about vertebral or hip shape, true volumetric density (g/cm^3) or bone mineral apparent density (BMAD) may be estimated. Computed tomography provides a volumetric density (vBMD) but is not widely used given the relatively higher radiation doses involved. Results can be expressed as standardised or "Z-scores". The Z-score is the number of SD an observed measurement is away from the expected value (based on reference data) for age. Other outcome measures were biochemical markers of bone turnover, fracture occurrence, and subjective outcomes such as pain and disability.

Quantitative data analysis was not undertaken because of study heterogeneity. Findings were summarised using tables and narrative synthesis.

RESULTS

Initially, 94 papers were identified and 35 were excluded from the review: low bone mineral density not associated with JIA, connective tissue disease or osteogenesis imperfecta (17 papers), no intervention (five papers), data published elsewhere (four papers), other intervention (three papers), abstracts later published as full studies (three papers), treatment of hypercalcaemia (one paper), review article (one paper), or adult patients (one paper). The case series reported by Cimaz *et al*¹⁹ included children from the cohort study conducted by Bianchi *et al*, as well as some additional children.

Effectiveness of bisphosphonates

Sixteen papers discussed the use of bisphosphonates in children with JIA (table 1) or other connective tissue diseases (table 2): one randomised controlled trial (RCT),²⁰ three controlled cohort studies,^{21–23} 11 case series,^{19 24–33} and one case report.³⁴

Characteristics of children

Seventy eight JIA children could be identified in the 16 effectiveness studies, and five additional children were classified as having corticosteroid induced osteoporosis. Two studies recruited children at risk of low BMD and fractures because of disease and long term corticosteroid treatment.^{20 26} The remaining studies recruited children with pre-existing poor bone health; four of these studies required a history of fragility fractures.^{19 21 23 25}

Interventions

The studies evaluated mainly alendronate^{19–21 27 28 32 33} and pamidronate,^{23–25 29 30 34} using a range of different doses, routes of administration, and cycle lengths. In eight studies, all children continued with their usual corticosteroid

treatment.^{19–21 23 25–28} Nine studies ensured that calcium and/or vitamin D intakes were adequate.^{19–21 23 26 28 31 33 34} Follow up was generally for 1–2 years.

Outcomes assessed

All 16 studies assessed bone status (tables 1 and 2). Children had low BMD at baseline with Z-scores below the expected values for age and sex matched children. Treatment with bisphosphonates increased bone density compared with baseline: the mean percentage increase in spine BMD ranged from 4.5% to 19.1%.

In the RCT, lumbar spine BMAD increased significantly from baseline in the alendronate treated group ($p = 0.013$), whereas there was little change in the placebo group.²⁰ Femoral shaft BMAD also increased but was not statistically significant. Bianchi *et al* recorded a statistically significant mean increase in BMD after one year compared with baseline of $14.9 \pm 19.8\%$ ($p < 0.002$) in treated children; the increase was smaller and non-significant for untreated children ($2.6 \pm 6.5\%$).²¹ Acott *et al* reported that treatment with pamidronate resulted in significantly increased spine aBMD Z-scores compared with baseline.²³ The control children had higher baseline Z-scores compared with the treated children and the Z-scores decreased during the study. Lepore *et al* recorded an 8% increase in aBMD of children treated with clodronate for one year compared with a 7% decrease in untreated children.²²

Although BMD continued to increase with continued treatment in most studies, the percentage increase declined with time in some studies. For example, there was a mean percentage increase in aBMD of $3.5 \pm 6.1\%$ ($p = 0.005$) after one year of treatment compared with baseline, but after two years the annual change in aBMD was $13.8 \pm 11.8\%$ ($p = 0.004$) and after three years it was $4.5 \pm 11.8\%$ ($p = 0.05$).²⁶

Nine studies with bisphosphonates^{19–21 23–25 29 31 34} evaluated the effect of treatment on biochemical markers of bone turnover including markers of bone formation such as osteocalcin and alkaline phosphatase, and markers of bone resorption such as pyridinoline, deoxypyridinoline, and the C-terminal and N-terminal cross-linked telopeptides of type I collagen. Four studies noted changes in these markers which were not consistent across studies,^{19–21 31} whereas five studies noted no significant changes.^{23–25 29 34}

Five studies reported the incidence of fractures before and after treatment.^{20 21 23 25 30} In the RCT, three subjects had sustained fractures before entering but during the study only one patient in the control group sustained a fracture.²⁰ In a second study, 17 children had experienced fracture on entry.²³ One of these children had a recurrence of a thoracic vertebral body compression fracture one year after discontinuation of pamidronate. In another study, 10 children had experienced 38 fractures in the year before treatment; 12 of these fractures had been in children with corticosteroid induced osteoporosis.²⁵ Only two fractures occurred in the first year of treatment with pamidronate and none of these were in children with corticosteroid induced osteoporosis. Bianchi *et al* reported that no new fractures occurred during treatment with alendronate.²¹ However, they did not report the incidence of fractures before treatment. In the fifth study, three of four children had fractures in both the lumbar and thoracic spine at baseline; there were no further vertebral fractures during the study.³⁰

Improvements in subjective outcomes were also noted, including a progressive reduction in chronic bone pain and disability,²⁴ reduced bone pain and increased strength,²⁵ resolution of back pain,²⁸ and immobilised children became able to walk.²⁹

Table 1 Bisphosphonate studies in connective tissue disease, including patients with JIA

Study	Intervention group	Age (mean $\pm$ SD) and sex	Bisphosphonate: dose and route	Control group	Age (mean $\pm$ SD) and sex	Follow up	Densitometry	Markers of bone turnover
Randomised controlled trial								
Rudge <i>et al</i> (2005) ²⁰	11 patients: JIA (2), SLE (6), autoimmune haemolytic anaemia (1), inflammatory bowel disease (1), renal transplantation (1); 10 completed study	9.9 $\pm$ 2.8 years 6 F, 5 M	Alendronate oral, 1–2 mg/kg body weight once weekly	11 patients: JIA (5), dermatomyositis (4), inflammatory bowel disease (1), cystic fibrosis (1); 8 completed study. Received placebo	8.5 $\pm$ 4.4 years 7 F, 4 M	1 year	DXA, BMAD estimated. Mean lumbar spine BMAD increased from 0.266 to 0.307 g/cm ³ ($p=0.013$) in the alendronate and from 0.255 to 0.276 in the placebo group. Mean femoral shaft BMAD increased from 1.06 to 1.09 g/cm ³ in the alendronate group and from 1.03 to 1.04 in the placebo group	N-telopeptide/creatinine ratio decreased significantly in the alendronate group after 12 months (299 to 148, $p=0.007$) but not in the placebo group (303 to 301)
Prospective cohort, controlled								
Acott <i>et al</i> (2005) ²³	17 patients with fractures while on corticosteroid therapy, JRA (1), dermatomyositis (1), polyarthritis (1), post renal transplant (2), rapidly progressive glomerulonephritis (5), nephrotic syndrome (2)	Age not reported 8 F, 9 M	Pamidronate iv, 1 mg/kg/dose (max 90 mg) once every 2 months for 1 (n=15) or 2 years (n=2)	17 patients. Matched for disease and corticosteroid exposure. Received standard treatment	Matched for age and sex	Treated for 1 or 2 years, followed up to 3 years post treatment	DXA. Control group had higher baseline lumbar spine aBMD than pamidronate group. With pamidronate, Z-scores increased ($F=11.27$, $p=0.0057$); by 30 or 36 months, 0.77 $\pm$ 0.71 v controls, -0.68 ± 0.25	Bone specific ALP and N-telopeptide/creatinine ratios did not significantly change during treatment
*Bianchi <i>et al</i> (2000) ²¹	38 patients: systemic JIA (7), polyarticular JIA (9), SLE (11), dermatomyositis (6), Bechet's syndrome (2), Wegener's granulomatosis (1), undefined connective tissue disease (2)	12.8 $\pm$ 3.6 years 26 F, 12 M	Alendronate oral, 5 mg daily for body weight $\leq$ 20 kg, 10 mg daily for $>$ 20 kg	38 patients: 19 JIA, 13 SLE, 6 dermatomyositis. Less severe disease not requiring corticosteroid therapy, no fractures. Tanner stage 1 (11), 2 (6), 3 (5), 4 (5), 5 (11), (11 menarche). Received standard treatment	Matched for age (12.3 $\pm$ 3.9 years) and sex (26 F, 12 M)	1 year	DXA, adjusted for body size. Patients: mean increase BMD = 14.9 $\pm$ 9.8% ($p<0.002$) compared with baseline. Controls: mean BMD increase = 2.6 $\pm$ 5%	In the alendronate group, serum bone specific ALP decreased by mean of 16.5 $\pm$ 10.8%, urinary excretion N-terminal cross-linked telopeptides of type I collagen (NTX) decreased by 27 $\pm$ 16.5%. In the control group, ALP increased from 223 $\pm$ 180 to 299 $\pm$ 157 units/L, NTX was not evaluated
Lepore <i>et al</i> (1991) ²²	JCA (7)	Not reported	Clodronate, oral 1200 mg/day	JCA (6). Received standard treatment		1 year	Computed tomography. Patients: lumbar spine mean vBMD increased from 129 mg/cm ³ to 134 mg/cm ³ (8% increase) Controls: from 123 mg/cm ³ to 115 mg/cm ³ (7% decrease)	Not evaluated/reported
Case series								
Noguera <i>et al</i> (2003) ²⁴	10 patients with rheumatic diseases and glucocorticoid-induced osteoporosis: JIA (8), SLE (1), dermatomyositis (1)	11.1 $\pm$ 4.7 years 8 F, 2 M	Pamidronate iv, 2–4 mg/kg body weight, cycle repeated every 6 months	None	Not applicable	4–12 cycles (2–6 years)	DXA. Before treatment lumbar spine aBMD Z-scores -1.87 to -4.73 . After treatment mean Z-score for 7 patients improved from -3.76 to -1.91 ($p<0.02$) (2–131% improvement)	Levels of serum ALP and osteocalcin were normal before treatment, no significant changes during the study

Table 1 Continued

Study	Intervention group	Age (mean $\pm$ SD) and sex	Bisphosphonate: dose and route	Control group	Age (mean $\pm$ SD) and sex	Follow up	Densitometry	Markers of bone turnover
*Cimaz <i>et al</i> (2002) ¹⁹	45 patients: systemic JIA (8), polyarticular JIA (10), SLE (14) dermatomyositis (7), other (6)	12.9 $\pm$ 3.8 years 31 F, 14 M	Alendronate oral, 5 mg/kg daily for body weight <20 kg and 10 mg/kg for body weight $\geq$ 20 kg	None	Not applicable	1 year	DXA, adjusted for body size. Lumbar spine BMD Z-score: median % change 34.08, mean absolute change 0.87 $\pm$ 0.57 ($p < 0.001$)	Statistically significant decrease in bone markers after 6 months of treatment which continued throughout 12 months: median % change N-terminal cross-linked telopeptides of type I collagen -40.27% ($p = 0.001$), pyridinaline -29% ($p < 0.001$), bone-specific ALP -40.77% ($p = 0.011$), osteocalcin -38.51% ($p = 0.006$)
Gandrud <i>et al</i> (2003) ²⁵	11 patients: JIA (1), corticosteroid-induced osteoporosis (4), OI (6)	9.9 $\pm$ 3.7 years 7 F, 4 M	Pamidronate iv, 1 mg/kg once every 3 months (maximum 30 mg)	None	Not applicable	3–30 months	DXA, BMAD estimated. Mean annualised increase in lumbar spine aBMD 20.1 $\pm$ 16.9%. Mean increase in BMD Z-scores 1.260 $\pm$ 0.943. Mean annualised increase in BMAD 15.1 $\pm$ 18.1%. Mean increase in BMAD Z-score 1.403 $\pm$ 1.209. BMD at other sites also improved	Serum ALP levels fluctuated in several children without a noticeable trend
†Gattinara <i>et al</i> (2000) ²⁶	25 patients on corticosteroid treatment: systemic JCA (7), polyarticular JCA (11), paucarticular JCA (4), SLE (3)	15.6 years, (range 7.8–25.0) 6 M, 19 F	Etidronate oral, 150–300 mg/day for 15 days followed by calcium citrate 0.5–1.0 g/day for 75 days on a cyclic course	None	Not applicable	6–36 months	DXA. Mean % change in lumbar spine aBMD in the year before start of treatment was -6.5% $\pm$ 5.0, 6 months: 3.4% $\pm$ 4.7 ($p < 0.0001$), 12 months: 3.5% $\pm$ 6.1 ($p = 0.005$), 24 months: 13.8% $\pm$ 11.8 ($p = 0.004$), 36 months: 4.5% $\pm$ 11.8 ($p = 0.05$)	Not evaluated/reported
Brumsen <i>et al</i> (1997) ²⁹	12 patients: JRA (1), idiopathic juvenile osteoporosis (1), idiopathic osteoporosis (5), OI (4), mitochondrial myopathy (1)	JIA: 10.7 years. All patients: 14.1 $\pm$ 2.2 years	JIA: pamidronate iv, 7.5 mg daily for 18 days, then oral pamidronate 300 mg/day All patients: oral and/or iv pamidronate, range of doses. Oral olpadronate	None	Not applicable	11.7 years	DPA, DXA. JIA (1 patient): lumbar spine aBMD at baseline Z-score = -3.7, increased with treatment to -1.1 (2.6%). All patients: aBMD increased at all sites measured	ALP and urinary hydroxyproline secretion decreased progressively in all children; final values were at the upper part of the normal adult range
Shaw <i>et al</i> (2000) ³⁰	5 patients: JIA (1), Cushing's syndrome (1), OI (1), liver transplant (1), idiopathic juvenile osteoporosis (1)	JIA: 10 years F All patients: 10–15 y 4 F, 1 M	Pamidronate iv, every 3 months Total dose over 1 year range 0.5–12 mg/kg	None	Not applicable	1 year	DXA. JIA: baseline lumbar spine aBMD = 0.444 g/cm ² . After 1 year, aBMD = 0.556 g/cm ² , % change 26%. All patients: aBMD and Z-scores increased	Not evaluated/reported

Table 1 Continued

Study	Intervention group	Age (mean $\pm$ SD) and sex	Bisphosphonate: dose and route	Control group	Age (mean $\pm$ SD) and sex	Follow up	Densitometry	Markers of bone turnover
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*The case series reported by Cimaz *et al*,¹⁹ included children from the cohort study conducted by Bianchi *et al*, as well as some additional children.

†Conference abstract.

JIA, juvenile idiopathic arthritis; International League against Rheumatism criteria; JRA, juvenile rheumatoid arthritis; American Rheumatism Association criteria; JCA, juvenile chronic arthritis; European League Against Rheumatism (EULAR) criteria; SLE, systemic lupus erythematosus; OI, osteogenesis imperfecta; DPA, dual photon absorptiometry; ALP, alkaline phosphatase.

Review of safety

JIA and connective tissue diseases

Three studies with bisphosphonates reported no side effects in children.^{27 28 33} Two studies reported gastrointestinal irritation with oral bisphosphonates;^{21 22} two children discontinued treatment and in one of these children, oesophageal erosions then healed.²¹ Four studies using intravenous administration of bisphosphonates reported an acute phase reaction or a transient flu-like reaction (fever, muscle aches, bone pain) after the first infusion; symptoms were generally managed with paracetamol or ibuprofen and did not occur with further infusions.^{24 25 29 30} Noguera *et al* observed mild abdominal pain, nausea, and vomiting after the first infusion.²⁴ In subsequent cycles, children received intravenous ondansetron before pamidronate and did not experience any further problems. Five studies reported that growth appeared normal during treatment with bisphosphonates.^{21 25 29 32 34}

Osteogenesis imperfecta

Forty three additional papers evaluated the use of bisphosphonates, mainly pamidronate, in children with osteogenesis imperfecta and were included in the safety review.^{35–77} As in JIA, the most common side effect of intravenous treatment was an acute phase reaction during the first infusion of bisphosphonate. Munns *et al* observed respiratory distress in four infants with severe osteogenesis imperfecta and pre-existing respiratory compromise during their first treatment with intravenous pamidronate.⁶¹

Eight studies reported transient decreases in calcium and phosphate levels after treatment with intravenous pamidronate.^{35 42 50 51 54 58 59 68} No symptoms of hypocalcaemia were reported and calcium levels returned to normal with or without supplementation. Hogler *et al*⁷⁷ recorded biochemical hypocalcaemia in 74% of children and hypophosphataemia in 82% of children after the first infusion of zoledronic acid. The decrease in calcium levels became less after the second and third infusions.⁷⁷ In one study, a girl with slightly increased serum calcium levels at the start of the study developed microcalcifications of the renal papillae after one year of treatment with intravenous pamidronate.⁴³ The calcium levels returned to normal after withdrawal of vitamin D supplements and the microcalcifications started to regress. Three studies noted no changes on renal ultrasound during treatment with intravenous pamidronate.^{46 47 56}

Several studies examined the effects of bisphosphonates on bone re-modelling and fracture healing. In one study, bone turnover was suppressed to below that of normal children.³⁵ Falk *et al*⁵⁵ observed non-union of a tibial fracture. During pamidronate treatment, Munns *et al*³⁶ observed significant delays in elective osteotomy site healing but non-significant delays in fracture healing, compared with before treatment. Two studies noted that fracture healing was not delayed and there were no instances of fracture non-union.^{42 70} The linear growth of children was at least normal in four studies.^{42 47 56 64} Sclerosis occurred at various bone sites which disappeared on discontinuation of treatment with pamidronate.⁵³ There were no effects of commonly used doses of bisphosphonates on the growth plate and the bone ages of children corresponded with their chronological age.⁴²

Two young women received long term pamidronate treatment before conception.⁶⁶ Pamidronate was stopped after conception; the pregnancies and deliveries were uneventful and both mothers and babies remained well up to 16 months postpartum.

DISCUSSION AND CONCLUSIONS

Evidence from the studies included in this review indicates that bisphosphonates may have a role in preventing low BMD

Table 2 Bisphosphonate studies in other connective tissue diseases

Study	Intervention group	Age (mean $\pm$ SD) and sex	Bisphosphonate: dose and route	Follow up	Densitometry	Outcome
Case series *Bardare <i>et al</i> (2000) ²⁷	6 patients with corticosteroid induced osteoporosis: SLE (5), dermatomyositis (1)	15.7 years (range 10.9–18.1) 5 F, 1 M	Alendronate oral 10 mg/day	2 years	DXA. After 1 year: mean increase in lumbar spine aBMD 19.1% (range 4.9 to 38%). After 2 years: mean improvement 6%	Not evaluated/reported
Falcini <i>et al</i> (1996) ²⁸	4 patients with rheumatic disease or drug induced osteoporosis: post-streptococcal (1), polyarteritis (1), lupus-like syndrome (1), dermatomyositis (1)	10 years 6 months, (range 6–13 years) 4 F	Alendronate infusion 3.25 mg/day for 3 consecutive days, second course 3 months later	1 year	DXA. Mean baseline lumbar spine aBMD = 0.654 g/cm ² (range 0.595 to 0.722 g/cm ²). After 12 months, mean = 0.764 g/cm ² (range 0.655 to 0.860 g/cm ²)	Not evaluated/reported
†Bayer <i>et al</i> (2002) ³³	9 patients: corticosteroid-induced osteoporosis (3) OI (6)	12.3 $\pm$ 1.7 years 7 M, 2 F	Alendronate oral 5 or 10 mg/day	12.9 $\pm$ 1.5 months	Baseline Z-scores were -4.2 ± 2.2 for lumbar spine and -2.3 ± 1.1 for total body. After 12 month's treatment: spine BMD increased to -3.1 ± 1.6 ($p < 0.02$) and total body aBMD to -2.0 ± 1.5 ($p < 0.2$)	Not evaluated/reported
Chlebna-Sokol <i>et al</i> (2003) ³¹	5 patients treated with bisphosphonates: OI (2), idiopathic osteoporosis (1), secondary osteoporosis (2)	Range 10.2–18.2 years 4 M, 2 F	Bisphosphonates	6 months to 12 months	DXA. Total body aBMD Z-score range, baseline: -3.76 to -1.43 , 6 months: -3.12 to -0.9 , 12 months: -2.90 to -0.90 Lumbar spine aBMD Z-score range, baseline: -5.09 to -3.00 , 6 months: -2.85 to -2.00 , 12 months -2.50 to -1.18	Decrease in C-terminal cross-linked telopeptide of type I collagen, osteocalcin levels fell in two children but increased in three children, dypyridinoline:creatinine and pyridinoline:creatinine ratios fell in most children
Case report Oliveri <i>et al</i> (1996) ³⁴	Dermatomyositis (1)	8 years F	Pamidronate oral, 4 mg/day	21 months	DXA. At baseline total body aBMD = 0.790 g/cm ² , Z-score = -2.1 . aBMD lumbar spine 0.533 g/cm ² , Z-score -3.6 . After 21 months, aBMD = 1.047 g/cm ² , Z-score = 1.0. Lumbar spine aBMD = 1.02 g/cm ² , Z-score = 0.43	Serum levels of ALP remained within normal range

*An abstract only was available from Embase, a full copy of the paper was not available from UK sources.

†Conference abstract.

OI, osteogenesis imperfecta.

and fragility fractures associated with JIA. However, the quality of the studies was variable. Only small numbers of children with JIA were included and studies recruited a mixture of children with JIA and other connective tissue diseases. Only one study reported that they used a standard definition of JIA.²¹ There was considerable variation in the doses and schedules of bisphosphonates. Some children had been treated with corticosteroids when they entered the study and continued with treatment, others were not. It is possible that concomitant treatment with calcium and/or vitamin D may have affected the outcome, but only nine studies ensured that the children received an adequate calcium and/or vitamin D intake.

Four studies included an intervention group of children treated with bisphosphonates and a control group of children receiving standard treatment.^{20–23} However, none of the studies compared directly the results of intervention and control groups; the results were only compared with the group's own baseline. There were also differences in disease severity between groups. Acott *et al* compared corticosteroid treated children who had experienced fractures with corticosteroid treated children who had not experienced fractures and had greater BMD.²³ Similarly, the control group of children recruited by Bianchi *et al* had less severe disease which did not require corticosteroid therapy and had not experienced fragility fractures.²¹

The current methods of assessment of treatment outcome all have limitations. Measurement of BMD using DXA was the most widely used outcome measure in these studies but careful interpretation of the results is required.⁷⁸ DXA estimates BMD as a two-dimensional ratio of the amount of bone and the area scanned (aBMD) rather than true three-dimensional density. aBMD increases with bone size because of the greater thickness of larger bones; it underestimates aBMD in small children and overestimates it in larger children and thus may be affected by the child's body size, pubertal stage, and, to a lesser extent, age and ethnic group.⁷⁸ Several methods are available to adjust aBMD to account for the size of children.⁷⁸ The observed increase in aBMD after treatment with bisphosphonates may, in part, be caused by changes in bone size related to growth and puberty, but only two studies in the review reported that they adjusted BMD for size,^{19, 21} while two estimated volumetric BMD.^{20, 25} The fact that adjustments may not have been made to account for the size of children undermines the validity of the results and makes it difficult to compare results between studies.

Eight studies examined biochemical markers of bone turnover and noted changes in levels during treatment. However, there is uncertainty about which markers best reflect bone status. In addition, few normative data are available for paediatric bone markers which are affected by age, sex, and puberty.

Both densitometry and bone markers are surrogate outcomes; the outcome of main interest and significance is reduction in fracture occurrence in the subjects as both children and adults. Although only short term studies have been conducted, several showed a reduction in fractures during treatment with bisphosphonates. Longer term studies are needed to show that these effects are sustained.

The review of safety showed that bisphosphonates were generally well tolerated in children. However, there is a report of iatrogenic osteopetrosis after administration of very high doses of intravenous pamidronate for "idiopathic hyperphosphatasia".⁷⁹ A major concern has been about long term effects. Although bisphosphonates have anti-resorptive effects on bone, there was no evidence of adverse long term effects at commonly used doses. Hoekman *et al* observed that all the biochemical markers of bone turnover returned to pretreatment levels after stopping bisphosphonate treatment,

What is already known on this topic

- Low bone mineral density and fragility fractures are complications of JIA, persisting into adulthood
- Bisphosphonates are effective in post-menopausal osteoporosis and corticosteroid induced osteoporosis in adults, but there are concerns about their effectiveness and long term adverse effects in children

What this study adds

- There are few studies of bisphosphonates in children with JIA overall, and only four comparative studies; the quality of evidence from these studies is variable
- Bisphosphonates appear to be a promising treatment for low bone mineral density and fragility fractures, but future studies in JIA should have longer follow up and more rigorous assessment of outcome

suggesting that there was no permanent inhibition of bone activity.⁸⁰ Several studies reported that fracture and osteotomy site healing was not delayed. Linear growth was unaffected by treatment. Sclerotic lines have occurred but they faded or disappeared, although a recently published study shows that they can persist for up to 8 years (mean 4 years).⁸¹ This study also noted that pamidronate interferes with the process of periosteal resorption, resulting in wider metaphyses.⁸¹ There have been concerns that bisphosphonates could be retained in bone then released later in life. Of note, two young women continued treatment with bisphosphonate until conception without untoward effects on themselves or their babies.⁶⁶ However, because of the different disease pathologies, some care should be taken with the extrapolation of results from the use of bisphosphonates in osteogenesis imperfecta to effects in children with JIA. For example, there are anecdotal reports of bone mineral density increasing with bisphosphonates, but after prolonged treatment the bones were found to be more brittle during spinal surgery.⁸² There is also concern that bisphosphonates administered at higher doses produce highly mineralised bone that is subject to microfracture damage,⁸³ which might potentially increase the risk of cortical fractures in the long term. The effects of long term accumulation of bisphosphonates in children are unknown.

In conclusion, bisphosphonates are a promising treatment for osteoporosis in children with JIA, but the quality of the current evidence is variable; better studies are needed to support evidence based practice in this patient group. The lack of evidence in this area reflects a wider gap in evidence available to support paediatric prescribing. The recent National Service Framework for Children recommends that children who require ongoing health interventions have access to high quality care.⁸⁴ This access is reduced by the lack of evidence to support prescribers in providing safe and effective treatments. Recognition of this gap has led to the development of the Medicines for Children Research Network which aims to improve the quality of research in this area (<http://www.liv.ac.uk/mcrn/>). Studies need to recruit larger numbers of more clearly defined patients. Outcome must be accurately assessed, taking into account both growth of children during the study and any technical limitations of the measures. A recent general review supports our findings that there are still many unanswered questions

about the use of bisphosphonates in children.¹⁶ The optimum dose and frequency of administration and the length of treatment have not been defined. The maximal bone mass gain that can be achieved is not known and it is not clear whether the positive effects of treatment continue over time. The criteria for initiating treatment need clarifying; should treatment be limited to children with pre-existing low BMD and/or fractures or include children thought to be at risk of these problems? Finally, future studies should be longer term and include fragility fractures as an outcome. Multicentre studies are more likely to achieve sufficient patient numbers to answer some of these questions about longer term treatment, including the change in fracture incidence.

Finally, more aggressive treatment of JIA with intra-articular corticosteroids and intravenous corticosteroid pulses may help avoid long term treatment with oral corticosteroids. In addition, increased and earlier use of disease modifying antirheumatic drugs such as methotrexate and cytokine inhibitors such as etanercept and infliximab might reduce the decline in BMD in these children.

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Funding: this project was funded by the NHS R&D Programme Health Technology Assessment Programme (03/43/04)

Competing interests: none

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health

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