A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management


CRD summary
This review, which aimed to assess the effectiveness and safety of bisphosphonates and calcium/vitamin D in children with juvenile idiopathic arthritis and low bone mineral density, concluded that bisphosphonates are a promising treatment, but that better quality research is needed to confirm this. The authors' conclusions are likely to be reliable.

Authors' objectives
To assess outcome measures and treatment costs in children with juvenile idiopathic arthritis (JIA) and low bone mineral density (BMD) and/or fragility fractures; to assess long-term bone health in adults with JIA; to assess evidence for the effectiveness and safety of bisphosphonates and calcium and/or vitamin D in children with JIA and low BMD. This abstract will only cover the last of these assessments.

Searching
MEDLINE (from 1966 to July 2005), EMBASE (from 1980 to July 2005), ISI Web of Science Proceedings (from 1990 to July 2005), the Cochrane Controlled Trials Register, the Cochrane Database of Systematic Reviews, DARE, NHS EED and HTA were searched; the search terms were reported. Studies from the International Conference on Children’s Bone Health (May 2005) were also searched, as was the Current Controlled Trials website. The references of included studies and review papers were checked for further relevant studies.

Study selection
Studies of any design, examining the safety or effectiveness of bisphosphonates (taken orally or by infusion), calcium and/or vitamin D in children (aged <18 years) with JIA and low BMD and/or fragility fractures were eligible for inclusion. Effectiveness studies also had to report any outcomes indicative of low BMD and/or fragility fractures, while safety studies had to report adverse events and safety. Safety studies of children with osteogenesis imperfecta were also eligible.

Of the included studies, 16 examined the effectiveness of bisphosphonates (alendronate, pamidronate, clodronate or etidronate) of varying doses, and two examined the use of calcium and/or vitamin D. Pamidronate was the main bisphosphonate used in the safety studies. Most of the effectiveness studies recruited children aged between 4 and 18 years, and most included more girls than boys. The majority of studies also recruited children with existing BMD problems. The outcomes assessed included bone densitometry, biochemical markers of bone turnover, adverse effects and the occurrence of fractures.

One reviewer selected studies for inclusion.

Assessment of study quality
A quality assessment tool was developed which could be used for all study types. This assessed evidence of bias in the areas of inclusion, selection, performance, attrition and detection.

One reviewer assessed the quality of the studies, with a second reviewer checking the assessment. Any differences were resolved by discussion.

Data extraction
Data on all relevant outcomes were extracted into tables which covered all study types.

One reviewer extracted the data, with a second reviewer checking the extraction. Any differences were resolved by
Methods of synthesis
Meta-analysis was not undertaken because of the clinical and methodological heterogeneity. A narrative synthesis was therefore undertaken, with differences between the studies discussed and study details tabulated.

Results of the review
Sixty-one studies (n=1,243) were included in the review, of which 43 were safety-only studies of children with osteogenesis imperfecta taking bisphosphonates (n=955), 16 were bisphosphonate studies (n=265), and 2 were calcium and/or vitamin D studies (n=23).

All of the studies were classed as being of a poor quality.

Effectiveness.
Of the 16 bisphosphonate studies, there was one randomised controlled trial (n=22), 3 controlled cohort studies (n=68), 11 case series (n=174) and 1 case report. Seventy-eight children had JIA. In all studies, bisphosphonate treatment increased BMD compared with baseline, with mean percentage increases in spine BMD varying from 4.5 to 19.1%. Five of the 9 studies reporting biochemical markers of bone turnover as an outcome reported no significant changes, while the other 4 studies reported decreases in markers. For the 2 studies of calcium and/or vitamin D, treatment resulted in increased BMD. Further results were reported.

Safety.
Follow-up periods in studies reporting safety data were generally between 1 and 4 years. In studies of bisphosphonate in children with JIA and connective tissue disease, three reported no side-effects, while others reported flu-like reactions, nausea and vomiting, or gastrointestinal side-effects. Studies of calcium and/or vitamin D did not report whether side-effects occurred during treatment. For studies of bisphosphonate in children with osteogenesis imperfecta, the most common side-effect reported with intravenous pamidronate was a transient flu-like reaction and bone pain; this was reported in 18 of the 43 studies (rates varied from 18 to 100%). Eight studies reported transient decreases in calcium and phosphorus levels.

Cost information
The mean annual total cost per child in the first year after diagnosis with JIA was £1,649. The highest cost component was appointments with paediatric rheumatologists.

Authors’ conclusions
Bisphosphonates are a promising treatment for osteoporosis in children with JIA, but the poor quality of current evidence means further assessment is required.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant studies were undertaken by searching electronic databases and other methods. However, the use of language restrictions was not reported, so it is difficult to comment on the possibility of studies not published in English being missed from the search. The use of only one reviewer to select studies for inclusion in the review means that the authors did not minimise the risk of reviewer error or bias affecting this process, although methods were used to avoid such risk in the quality assessment and data extraction processes. Study quality was assessed, and was used in interpreting the results of the review. Sufficient study details were provided and an appropriate narrative synthesis of the data was undertaken. The authors’ conclusions are suitably cautious in reflecting the poor quality of the evidence available, and are likely to be reliable.

Implications of the review for practice and research
Practice: Bisphosphonates may have a role in the prevention and treatment of low BMD and fragility fractures in
children with JIA.

Research: Better-designed longer-term studies are needed to confirm the potential benefits of bisphosphonates in the prevention and treatment of low BMD and fragility fractures in children with JIA.

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