The efficacy of bisphosphonates in the prevention of vertebral, hip, and nonvertebral-nonhip fractures in osteoporosis: a network meta-analysis

Jansen JP, Bergman GJ, Huels J, Olson M

CRD summary
The review concluded that, in women with osteoporosis, zoledronic acid had the highest probability of preventing vertebral fractures and was comparable with alendronate in preventing hip fractures; risedronate was superior in preventing non-vertebral and non-hip fractures. The potential for biases within the review and the uncertain quality of included trials mean that caution is warranted when interpreting the authors’ conclusions.

Authors' objectives
To evaluate the efficacy of available bisphosphonates in the prevention of vertebral, hip, and non-vertebral/non-hip fractures in postmenopausal women with osteoporosis.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched from October 2002 to June 2007 for articles published in English. Search terms were reported. A previous review (see Other Publications of Related Interest) was used to identify relevant articles published before October 2002.

Study selection
Randomised controlled trials (RCTs) of bisphosphonates (zoledronic acid, alendronate, risedronate, ibandronate or etidronate) versus placebo for the prevention of fractures in postmenopausal women with osteoporosis were eligible for inclusion. Trials had to be double-blind and had to have at least a three year follow-up period (two years if used for registration purposes). Trials could study more than one bisphosphonate agent or dose. The relevant outcomes measures were vertebral fractures, hip fractures, and non-vertebral/non-hip fractures. Abstracts and letters were excluded.

The included trials evaluated zoledronic acid (5mg), alendronate (5 to 20mg), risedronate (5mg), ibandronate (2.5mg daily; 20mg intermittent) or etidronate (400mg intermittent) versus placebo. All trials had calcium as a background treatment (500 to 1500mg), and six to eight trials also had vitamin D supplementation (250-1200 IU). The mean age of participating women ranged from 64 to 73 years; the number of years since the menopause varied from two to 25 years. Lumbar spine bone mineral density ranged from 0.68 to 0.85g/cm².

Two reviewers independently performed study selection.

Assessment of study quality
The authors did not state if they assessed trial quality.

Data extraction
Data were extracted on the incidence of hip, vertebral, and non-vertebral/non-hip fractures, and used to calculate relative risks (RRs), with 95% credible intervals (CrIs).

Two reviewers independently performed data extraction.

Methods of synthesis
A fixed-effect Bayesian network (mixed-treatments) meta-analysis was used to calculate pooled relative risks with 95% credible intervals for comparative relative risks for each bisphosphonate versus placebo and indirect pair-wise comparisons of bisphosphonates. The probability that a treatment was associated with a 10% and 20% reduction in fracture risk was also calculated for each comparison. Sensitivity analysis were performed weighting the impact of fracture reduction according to specified criteria.
Results of the review
Eight RCTs were included in the review (n>20,000 women), comprising two newer trials and six trials from the Stevenson review. The sample size ranged from 423 to 7,736 women. Treatment duration ranged from two to four years (median of three years).

Vertebral fractures: Zoledronic acid had a 79% probability of the greatest reduction in vertebral fractures. Zoledronic acid was superior to placebo (RR 0.30, 95% CrI 0.23 to 0.37). Indirect analyses indicated that zoledronic acid was superior to alendronate (RR 0.55, 95% CrI 0.41 to 0.76), risedronate (RR 0.50, 95% CrI 0.36 to 0.70), and ibandronate (RR 0.58, 95% CrI 0.37 to 0.92). The probability of a greater than 20% risk reduction ranged from 97% to over 99%.

Hip fractures: Zoledronic acid had a 47% probability of offering the greatest reduction in hip fractures, followed by alendronate (37%). The relative risk of zoledronic acid versus alendronate was 0.95 (95% CrI 0.54 to 1.68).

Non-vertebral/non-hip fractures: Risedronate had a 87% probability of the greatest reduction in fractures. The relative risk of zoledronic acid versus risedronate was 1.28 (95% CrI 0.87 to 1.90).

Other results and sensitivity analyses (weighted by various factors) were presented in the review.

Authors' conclusions
In women with osteoporosis, zoledronic acid had the highest probability of offering the best vertebral fracture protection. It was comparable with alendronate in preventing hip fractures, but was not as efficacious as risedronate in preventing non-vertebral and non-hip fractures.

CRD commentary
Inclusion criteria for the review were clearly defined. Several relevant databases were searched. There was the potential for language bias, as only English language articles were included. Publication bias was not assessed and could not be ruled out. Attempts were made to reduce reviewer error and bias throughout the review process.

The authors did not state if quality assessment was undertaken, but their inclusion was limited to double-blind trials, which should have ruled out very low quality trials. However, the quality of the included trials remained unclear. Trials were combined using fixed-effect mixed treatments meta-analysis; the authors provided suitable justification for the choice of model.

Overall, the potential for biases within the review and the uncertain quality of included trials mean that the authors’ conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: Weighting vertebral, hip, and non-vertebral/non-hip fractures by their impact on cost, quality of life and incidence, zoledronic acid (5mg) was the bisphosphonate expected to provide the greatest benefit overall.

Research: The authors did not state any implications for research.

Funding
Novartis Pharmaceuticals (manufacturers of zoledronic acid).

Bibliographic details

PubMedID
20828791
DOI
10.1016/j.semarthrit.2010.06.001

Original Paper URL
http://dx.doi.org/10.1016/j.semarthrit.2010.06.001

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Bone Density Conservation Agents /therapeutic use; Diphosphonates /therapeutic use; Female; Hip Fractures /prevention & control; Humans; Osteoporotic Fractures /prevention & control; Postmenopause; Randomized Controlled Trials as Topic; Spinal Fractures /prevention & control; Treatment Outcome

AccessionNumber
12011001386

Date bibliographic record published
06/07/2011

Date abstract record published
28/09/2011

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.