Clinical efficacy and safety of denosumab in postmenopausal women with low bone mineral density and osteoporosis: a meta-analysis


CRD summary
This review demonstrated a significant reduction in relative fracture risk in the denosumab group, compared to the placebo group. The reliability of the authors' conclusion is restricted by the fact that most participants were in the lowest quality trial, and problems with such data are unknown due to the limited validity assessment undertaken.

Authors' objectives
To assess the clinical efficacy and safety of denosumab for postmenopausal women with low bone mass.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched until February 2010 without language restrictions (search terms were reported). Bibliographies of reviews identified through the search were handsearched to locate further studies.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared the efficacy and safety/tolerability of denosumab versus placebo for treatment of low bone mineral density or osteoporosis in postmenopausal women. The efficacy-related outcome was overall incidence of fractures in the treatment and control groups; safety or tolerability outcomes included overall incidence of serious adverse events, incidences of serious adverse events relating to infection and neoplasms and the percentage of study discontinuations resulting from serious adverse events. Trials that contained men and/or participants with conditions that influence bone metabolism were excluded.

All trial participants were female and most were reported as being postmenopausal (one trial described 73% of its participants as postmenopausal). Mean age ranged from 59.4 to 72.3 years. Bone mass density T-scores ranged from less than or equal to -2.5 to more than or equal to -4.0. All included trials were RCTs with placebo control treatments; most participants received a maximum denosumab dosage of 60mg/six months. Primary outcomes included incidence of new vertebral fractures and lumbar spine bone mass density at 12 months or 24 months. Secondary outcomes were reported fully in the paper.

Two reviewers independently screened the studies for inclusion; differences were resolved through discussion and consensus.

Assessment of study quality
Study quality was assessed according to quality of description for methods used to generate randomisation sequences, double blinding and reporting of withdrawals and drop-outs, using the Jadad Scale (on a scale of one to five, where five was the highest quality).

Quality assessment was performed independently by two reviewers; differences were resolved through discussion and consensus.

Data extraction
Data were extracted to enable the calculation of risk ratios and 95% confidence intervals for incidence of fractures and outcomes related to serious adverse events, including mortality and discontinuations. Adverse event outcomes were examined using an on-treatment analysis (defined in the paper).

Data were extracted by two independent reviewers; differences were resolved through discussion and consensus.

Methods of synthesis
Risk ratios (RRs) were pooled in a fixed-effect (Mantel-Haenszel) or random-effects meta-analysis alongside 95%
confidence intervals (CIs), according to the level of statistical heterogeneity observed. Where there was evidence of significant statistical heterogeneity (assessed using $X^2$ and $I^2$), sensitivity analyses were performed to investigate the impact of excluding a study with an atypical population, and of using data from a different time point in another study.

**Results of the review**

Four RCTs (8,864 participants) were included in the review and meta-analysis; study sample size ranged from 252 to 7,868 participants. Trials scored 3 (one trial), 4 (two trials) and the maximum score of 5 (one trial) for quality with the Jadad Scale.

Fracture risk was statistically significantly lower for postmenopausal women in the denosumab group, compared with the placebo group (RR 0.58, 95% CI 0.52 to 0.66, $I^2=15\%$, three trials).

No statistically significant differences between denosumab and placebo groups were found for risk of serious adverse events, serious adverse events related to infection, neoplasm, study discontinuation due to adverse events, and mortality (reported fully in the paper).

Sensitivity analyses revealed statistically similar findings for all of the outcomes (reported fully in the paper).

**Authors' conclusions**

This review demonstrated a significant reduction in relative fracture risk in the denosumab group, compared to the placebo group.

**CRD commentary**

The review question was clear and inclusion criteria seemed replicable. Appropriate electronic databases were accessed and attempts appeared to have been made to minimise language bias. Publication bias was possible but could not be assessed due to the small number of studies included. The review process included attempts to minimise reviewer error and bias for study selection, data extraction and quality assessment.

The authors assessed quality using a tool which used some relevant criteria, but only reporting summary scores was not very useful in forming a clear picture of study quality. The largest trial, which contained most of the participants, had the lowest quality score. Study characteristics were presented; methods of synthesis seemed appropriate and attempts to were made to explore clinical and methodological heterogeneity between trials. The reliability of the authors’ conclusion is restricted by the fact that most participants were in the lowest quality trial, and problems with such data are unknown due to the limited validity assessment undertaken.

**Implications of the review for practice and research**

**Practice:** The authors stated that denosumab could be an effective new treatment for osteoporosis with fewer adherence barriers than present treatments.

**Research:** The authors stated that data on continued long-term use of denosumab were necessary to capture its full effect on incidence of infections, neoplasms and mortality.

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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.