Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis
Anastasilakis AD, Toulis KA, Goulis DG, Polyzos SA, Delaroudis S, Giomisi A, Terpos E

CRD summary
The authors concluded that denosumab had not yet proved its efficacy on fracture risk reduction in postmenopausal women with osteopenia/osteoporosis and increased infection risk questioned its safety. This conclusion reflected the evidence presented. However, given the small number of included studies and deviation from some inclusion criteria, the results of the review should be interpreted with caution.

Authors' objectives
To determine the efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions from inception to January 2009. Search terms were reported. Conference abstracts and references of relevant trials and systematic reviews were searched and experts contacted in order to identify unpublished studies.

Study selection
Randomised controlled trials (RCTs) that compared the efficacy and safety/tolerability of 60mg denosumab every six months to placebo for the treatment of low bone mass (osteopenia or osteoporosis) in postmenopausal women were eligible for inclusion in the review. Trials were excluded if they included women diagnosed with metastatic bone disease. Outcomes of interest included risks of clinical fracture, serious adverse events, serious infection, neoplasm and drop-out due to adverse event. Mortality rate was an additional outcome.

The average age of women was similar in the included studies (57.3 years to 63.1 years). The dose of denosumab was 60mg every six months for 24 months in two trials. Despite the stipulated inclusion criteria, one trial included men. The dose of denosumab was 6mg, 14mg or 30mg for three months and 14mg, 60mg, 100mg or 210mg for six months in another trial. A third trial used an active rather than placebo control. In two studies women had osteopenia or osteoporosis and in a third women had non-metastatic breast cancer and received aromatase inhibitors.

Two reviewers independently selected studies for inclusion in the review. Any discrepancies were resolved by a third reviewer.

Assessment of study quality
Two reviewers independently assessed study quality using the Jadad scale of randomisation, double blinding, withdrawal and drop outs. Any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted data in order to calculate the odds ratios (ORs) with 95% confidence intervals (CI) for death. Any disagreements were resolved by consensus. Authors were contacted in order to obtain missing data.

Methods of synthesis
Studies were grouped by outcome and pooled odds ratios were calculated using a fixed-effect or random-effects model. Heterogeneity was assessed using $X^2$ and $I^2$ tests. Publication bias was assessed with g funnel plots. Number needed to harm (NNH) was calculated for safety/tolerability outcomes.

Results of the review
Three studies (n=996 participants) were included in the analysis. All studies were of high quality (scored 4 on the Jadad scale).

Denosumab was not associated with a statistically significant reduction in fracture risk (OR 0.74, 95% CI 0.33 to 1.64;
three studies). There was no evidence of statistically significant heterogeneity or publication bias.

Denosumab was associated with a statistically significant increased risk of serious adverse events (OR 1.83, 95% CI 1.10 to 3.04, NNH 20, 95% CI 9 to 150; three studies) and serious infections (OR 4.45, 95% CI 1.15 to 17.14, NNH 50, 95% CI 12 to 1,119; three studies).

There was no statistically significant difference in in mortality rate or risk of neoplasm and drop-out due to adverse event. There was no evidence of statistically significant heterogeneity or publication bias.

**Authors' conclusions**
Denosumab had not yet proved its efficacy on fracture risk reduction and increased infection risk questioned its safety.

**CRD commentary**
The review addressed a clear research question. Inclusion criteria were clearly specified; however, the reviewers did not strictly adhere to these criteria when selecting studies for inclusion in the review. The search strategy was adequate, had no language restrictions and included attempts to locate unpublished material, which reduced risks of language and publication biases. The study quality assessment tool used was appropriate for the included study design; however, the authors gave an overall score and did not report scores for individual quality criteria. Adequate details of the primary studies were provided and the method of synthesis was appropriate. The authors highlighted a number of factors that affected the reliability of the results. These included inclusion of a study in which patients received various doses of denosumab, inclusion of a study in which patients had non-metastatic breast cancer as well as osteopenia and that all studies were industry sponsored. Review processes were conducted in duplicate, which reduced the risk of reviewer error and bias.

The authors’ conclusion reflected the evidence presented. However, given the small number of included studies and deviation from some inclusion criteria, the results of the review should be interpreted with caution.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that larger randomised controlled trials of denosumab for fracture risk reduction in postmenopausal women with osteopenia or osteoporosis were required.

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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.