Teriparatide (recombinant human parathyroid hormone 1-34) in postmenopausal women with osteoporosis: systematic review

Fernandes Moca Trevisani V, Riera R, Mizusaki Imoto A, Saconato H, Atallah A N

CRD summary
The authors concluded that intermittent low-dose teriparatide reduced vertebral and non-vertebral fractures and increased mineral bone density in postmenopausal women, but further long-term safety research was required. The authors’ conclusions appeared to reflect the results, but small sample sizes for some comparisons and unknown study quality made it difficult to assess their reliability.

Authors’ objectives
To evaluate the effectiveness and safety of teriparatide (recombinant human parathyroid hormone 1-34) for the treatment of postmenopausal osteoporosis.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, LILACS and congress abstracts in the areas of rheumatology, orthopaedics and bones were searched. Search dates varied across sources and spanned 1996 to January 2005. Search terms were reported. Pharmaceutical companies were contacted for unpublished data.

Study selection
Randomised controlled trials (RCTs) that evaluated the effect of teriparatide on bone mineral density and fractures in women with a natural or surgically-induced menopause and osteoporosis were eligible for inclusion. Studies could compare teriparatide with placebo, hormone replacement therapy, biphosphonates, calcitonin or calcium plus vitamin D. Studies had to assess bone mineral density using DEXA (dual-energy x-ray absorptiometry) and/or QCT (quantitative computed tomography) and report the number of vertebral and non-vertebral fractures and toxicity (including treatment withdrawals due to adverse events).

The included studies compared the following agents: subcutaneous teriparatide (20μg and 40μg) versus placebo; subcutaneous teriparatide (40μg) versus oral alendronate (10μg); teriparatide (400 units or 25μg) plus oestrogen versus oestrogen; and teriparatide (500 units or 40μg) plus nafarelin acetate versus nafarelin acetate. Participants included women with previous non-traumatic fractures, bone mineral density at least 1 or 2.5 standard deviations below the mean and women with endometriosis. Duration of follow-up ranged from six to 36 months.

Two reviewers independently selected studies.

Assessment of study quality
Two reviewers independently assessed validity using the Jadad criteria (randomisation, blinding and reporting of withdrawals).

Data extraction
Dichotomous data were reported as relative risks with 95% confidence intervals (CI); weighted mean differences were used for continuous data. Two reviewers extracted data. Differences were resolved with the help of a third reviewer.

Methods of synthesis
The authors stated that they planned to conduct sensitivity analyses, but no meta-analyses were presented. The studies were grouped by comparator and combined in narrative synthesis.

Results of the review
Four RCTs were included (n=1,867).

Teriparatide versus placebo (one RCT, n=1,637):
Teriparatide was associated with a statistically significant reduction in new vertebral fractures (relative risk 0.35, 95% CI: 0.22 to 0.55 with 20μg and relative risk 0.29, 95% CI: 0.18 to 0.48 with 40μg) and new non-vertebral fractures (relative risk 0.54, 95% CI: 0.37 to 0.79 with 20μg and relative risk 0.5, 95% CI: 0.34 to 0.74 with 40μg).

Teriparatide was associated with a statistically significant increase in whole-body bone mineral density (relative risk 3.1, 95% CI: 1.65 to 4.55 with 20μg and relative risk 4.5, 95% CI: 2.78 to 6.22 with 40μg), lumbar bone mineral density (relative risk 9.6, 95% CI: 7.79 to 9.41 with 20μg and relative risk 12.6, 95% CI: 11.62 to 13.58 with 40μg) and femoral bone mineral density (relative risk 3.6, 95% CI: 2.75 to 4.45 with 20μg and relative risk 4.6, 95% CI: 3.71 to 5.49 with 40μg).

There was no significant difference between teriparatide 20μg and 40μg in whole-body bone mineral density, femoral bone mineral density and rates of treatment withdrawal. Treatment withdrawal was significantly higher with teriparatide 40μg compared to placebo and with teriparatide 40μg compared to 20μg. Headache, nausea cramps, hypercalcaemia and the formation of anti-PTH (parathyroid hormone) antibodies were significantly more common in the teriparatide treatment groups.

**Teriparatide versus alendronate (one RCT, n=146):**

There was no significant difference between teriparatide and alendronate in the rate of new vertebral or non-vertebral fractures. Teriparatide was associated with an increase in whole-body and lumbar column and femur bone mineral density (results data and the statistical significance of this increase were not reported). The following adverse events were more common in the teriparatide treatment group: cramps; elevated serum and urinary calcium. Alendronate was associated with an increase risk of worsening lumbar pain.

**Teriparatide plus oestrogen versus oestrogen (one RCT, n=34):** Teriparatide plus oestrogen was associated with significant reduction in new vertebral fractures (relative risk 0.15, 95% CI: 0.03 to 0.73).

**Teriparatide plus nafarelin versus nafarelin (one RCT, n=50):** Bone mass increased by 3.4% in the teriparatide plus nafarelin group and by 3.5% in the nafarelin only group.

**Cost information**
The authors reported that teriparatide costs US$14,000 dollars for two years.

**Authors' conclusions**
Intermittent low-dose teriparatide reduced vertebral and non-vertebral fractures and increased mineral bone density in the lumbar column and femur in postmenopausal women. Further long-term safety research was required.

**CRD commentary**
The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched and attempts were made to minimise publication bias. It was unclear whether attempts were made to minimise language bias. Appropriate methods were used to minimise reviewer error and bias during the review process. Only RCTs were included and validity was reputedly assessed, but results of the validity assessment were not reported and so the quality of the studies was unknown. In view of the small number of studies that used different controls, a narrative synthesis was appropriate. The conclusion referred to intermittent regimens, but it was not clear from the paper that intermittent dosing regimens were indeed used. In addition, results data and levels of statistically significance were not consistently presented, so it was not possible to verify all findings reported in the review. The authors' conclusions appeared to reflect the results, but small sample sizes for some comparisons and unknown study quality made it difficult to assess their reliability.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further long-term research was required to assess the safety and the duration of the teriparatide treatment effect.
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