Reduction in the risk of developing back pain persists at least 30 months after discontinuation of teriparatide treatment: a meta-analysis


CRD summary
This review concluded that patients with osteoporosis treated with teriparatide have a reduced risk of developing back pain up to 30 months after treatment. The manufacturer of teriparatide funded the review, sponsored the included studies and employed three of the authors. Important systematic review methods that help ensure the findings are reliable were not mentioned in the report.

Authors' objectives
To evaluate the risk of back pain occurring or worsening up to 30 months after the discontinuation of teriparatide treatment for osteoporosis.

Searching
MEDLINE (1996 to 2006) and EMBASE (1988 to 2006) were searched; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Blinded randomised controlled trials (RCTs) with at least 30 months' observational follow-up were eligible for inclusion (observation in the follow-up phase was not blinded).

Specific interventions included in the review
Studies that compared teriparatide with placebo or another comparator were eligible for inclusion. The included studies compared teriparatide (20 or 40 microg/day) with placebo, alendronate (10 mg/day) or hormone replacement therapy. All participants received calcium and vitamin D supplementation. During the follow-up phase approximately 55% of the participants who received teriparatide in the trials were treated with another osteoporosis treatment, compared with approximately 64% of those who had received the comparator.

Participants included in the review
Studies in people with osteoporosis, who were free of other chronic conditions, were eligible for inclusion. The included studies enrolled either men or women but not both; approximately 80% of the participants overall were women. The mean age in the study groups ranged from 57.6 years (standard deviation, SD=13.2) to 69.4 years (SD=6.8).

Outcomes assessed in the review
The primary outcome in the included studies was vertebral fracture or bone mineral density, but the outcome assessed in this review was back pain observed during follow-up. The median follow-up in the included studies ranged from 29.7 to 30.4 months (the lowest interquartile range limit was 28.7 and the highest 31.7). Back pain was self-reported by the participants (study investigators systematically monitored adverse events during follow-up without specifically enquiring about back pain). Back pain severity was categorised as mild, moderate or severe (defined in the report).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
Individual patient data which the sponsor of the included studies had on file were used for the analysis. The number of years from the date of randomisation to the first occurrence of back pain (time-to-event) or the last date of follow-up was used to calculate the patient-years at risk for back pain for each patient. Back pain severity was determined as the first occurrence of the maximum severity category reported at any time after randomisation (after which patients were censored).

Methods of synthesis
How were the studies combined?
Analysis was by intention-to-treat. A Cox proportional hazards regression, stratified by trial and adjusted for the use of other osteoporosis drugs during follow-up, was used to calculate the hazard ratio as an estimate of the relative risk (RR) of back pain in the pooled teriparatide group versus the pooled control group. The RR in the individual studies was estimated using the same model without stratification. Meta-analysis was used to obtain pooled estimates of the RR with 95% confidence intervals (CIs). Kaplan-Meier methods were used to calculate the cumulative proportion of patients with new or worsening back pain in the pooled teriparatide and control groups, and to determine the first time of significant separation of back pain between the two groups (in units of 1 month).

How were differences between studies investigated?
Heterogeneity between the trials was investigated using a Cox regression model (p<0.1 considered statistically significant). A sensitivity analysis was conducted by serially excluding each individual study from the meta-analysis to assess the impact of individual studies. Meta-analysis was conducted for the subgroups of placebo-controlled trials and trials with an antiresorptive therapy comparator.

Results of the review
Four multicentre double-blind parallel RCTs (1,913 participants) were included.

A meta-analysis of all 4 trials (n=1,913) showed a significant reduction in the development of any back pain (RR 0.73, 95% CI: 0.61, 0.87), moderate or severe back pain (RR 0.72, 95% CI: 0.58, 0.89) and severe back pain (RR 0.39, 95% CI: 0.25, 0.61) in the teriparatide group compared with the control group. There was no statistically significant heterogeneity. The sensitivity analysis showed the results were robust to the removal of each individual study. A subgroup analysis of 2 placebo-controlled trials (n=1,617) gave similar results. In the subgroup analysis of 2 antiresorptive therapy comparator trials (n=296) the difference between teriparatide and control failed to reach statistical significance for moderate or severe back pain.

The cumulative proportion of patients who experienced back pain was significantly lower in the pooled teriparatide group compared with the pooled control groups from baseline through to 30 months’ follow-up (p<0.001), and the first significant separation between the two groups occurred at 6 months (p<0.05).

Authors’ conclusions
Teriparatide reduced the risk of patients with osteoporosis developing back pain during 30 months of post-treatment follow-up compared with placebo, alendronate and hormone replacement therapy.

CRD commentary
The review had a clear objective although the inclusion criteria appeared to be largely determined by the studies already known to the authors (see Other Publications of Related Interest). The review was funded by the manufacturer of teriparatide, also the sponsor of the included studies, and three of the authors were employees of the company. The search to identify relevant studies was not extensive and there was no information about restrictions on language, publication status or the screening procedure. There was insufficient information on study quality to make an independent assessment of the potential for bias in the included studies.

The data handling and analysis methods appeared appropriate (and were strengthened by the authors having access to
the individual patient data) but some aspects were not reported, such as weighting in the meta-analysis (presumably by trial variance). The meta-analysis graphs suggested a possible unit of analysis error (possibly artificially inflating the power) if the control group participants in the trials with more than one treatment arm (different doses) were included more than once, but it was impossible to be certain. How familiar the authors were with the data (which they already had on file) before planning the analysis was not known. The authors’ conclusion with regard to the non-placebo comparators was not fully supported (in terms of statistical significance) by their subgroup analyses. Overall, key aspects of systematic review methods were absent from the report and the authors’ conclusions might not be entirely impartial.

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

The authors did not state any implications for practice or further research.

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