

Denosumab, raloxifene, romosozumab and teriparatide to prevent osteoporotic fragility fractures: a systematic review and economic evaluation

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Scientific summary

Non-bisphosphonates to prevent fragility fractures

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Background

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in susceptibility to fragility fracture (defined by the World Health Organization as a broken bone resulting from a fall from standing height or lower). In the UK, the number of women and men aged > 50 years with osteoporosis has been estimated as 2,527,331 women and 679,424 men, with approximately 536,000 new fragility fractures, comprising 79,000 hip fractures, 66,000 vertebral fractures, 69,000 forearm fractures and 322,000 other fractures. Osteoporotic fractures cause significant pain, disability and loss of independence, and can be fatal.

Objectives

The objectives were to determine the clinical effectiveness and cost-effectiveness of denosumab (Prolia®; Amgen Inc., Thousand Oaks, CA, USA), raloxifene (Evista®; Daiichi Sankyo Company, Ltd, Tokyo, Japan), romosozumab [Evenity®; Union Chimique Belge (UCB) S.A. (Brussels, Belgium) and Amgen Inc.] and teriparatide (Forsteo®; Eli Lilly and Company, Indianapolis, IN, USA) within their licensed indications, for the prevention of osteoporotic fragility fractures, compared with each other, bisphosphonates or a non-active treatment.

Methods

A systematic review and network meta-analysis of clinical effectiveness and safety evidence for interventions of interest were conducted. Nine electronic databases (including MEDLINE, EMBASE and the World Health Organization International Clinical Trials Registry Platform) were searched up to July 2018. Studies were eligible for inclusion if they were randomised controlled trials comparing the non-bisphosphonates denosumab, raloxifene, romosozumab or teriparatide with each other, placebo or bisphosphonates within their licensed indication for an osteoporosis population, and reported either fracture or bone mineral density data. The quality of included studies was assessed using the Cochrane risk-of-bias tool.

A review of the existing cost-effectiveness literature was undertaken, including economic evaluations described in the company submissions. The identified cost-effectiveness analyses were compared with the model that was developed to inform the National Institute for Health and Care Excellence Multiple Technology Appraisal of bisphosphonates [National Institute for Health and Care Excellence. *Bisphosphonates for Treating Osteoporosis. Technology Appraisal Guidance [TA464]*. 2017. URL: www.nice.org.uk/guidance/ta464/resources/bisphosphonates-for-treating-osteoporosis-pdf-82604905556677 (accessed 20 November 2018)] to identify areas of difference. The model used in Technology Appraisal Guidance 464 was then adapted to evaluate the cost-effectiveness of non-bisphosphonates when compared with either no treatment or treatment with bisphosphonates across the whole population eligible for fracture risk assessment {as defined by the National Institute for Health and Care Excellence Clinical Guideline 146 [National Institute for Health and Care Excellence. *Osteoporosis: Assessing the Risk of Fragility Fracture. Clinical Guideline [CG146]*. 2012. URL: www.nice.org.uk/guidance/cg146/resources/osteoporosis-assessing-the-risk-of-fragility-fracture-pdf-35109574194373 (accessed 20 November 2018)]}. Incremental analyses were conducted for 10 risk categories based on deciles of risk when using either the QFracture® (QFracture-2012 open source revision 38, Clinrisk Ltd, Leeds, UK) or FRAX® (web version 3.9, University of Sheffield, Sheffield, UK) risk-scoring algorithms to determine risk.

In the economic analyses, treatment with romosozumab was modelled as a treatment sequence of romosozumab followed by the bisphosphonate alendronate (romosozumab/alendronate). All of the other treatment strategies modelled consisted of a single intervention followed by no treatment.

Results

The systematic review of clinical effectiveness identified 7898 citations. Fifty-two randomised controlled trials of non-bisphosphonates were included in the review, and an additional 51 randomised controlled trials of bisphosphonates were included for the network meta-analyses. Studies varied in quality, particularly on the domains of blinding and attrition, and were not all well reported.

Across studies reporting overall mortality, there were no significant differences between non-bisphosphonate treatment arms and their comparators of placebo, other non-bisphosphonates or bisphosphonates. The ranges of serious adverse event rates were as follows: denosumab, 1.6–25.8%; raloxifene, 2.0–18.6%; romosozumab, 3.2–12.9%; and teriparatide, 0.0–33.0%.

Network meta-analyses were conducted for vertebral fractures (46 randomised controlled trials, 11 interventions), non-vertebral fractures (42 randomised controlled trials, 11 interventions), hip fractures (23 randomised controlled trials, nine interventions), wrist fractures (15 randomised controlled trials, eight interventions), proximal humerus fractures (13 proximal humerus fractures, eight interventions) and percentage change in femoral neck bone mineral density (73 proximal humerus fractures, 12 interventions). For vertebral, non-vertebral and hip fractures and for femoral neck bone mineral density, all treatments were associated with beneficial effects relative to placebo. For both vertebral fractures and percentage change in femoral neck bone mineral density, the treatment effects were statistically significant at a conventional 5% level for all treatments. For vertebral, non-vertebral and hip fractures, teriparatide provided the largest treatment effect, although, in general, the ranking of treatments varied for the different outcomes. For wrist and proximal humerus fractures, there was less randomised controlled trial evidence, and so there is considerable uncertainty in treatment effects for certain interventions in these networks. Sensitivity analyses conducted to assess the impact of assessment method for vertebral fractures (radiographic or clinical), duration of study, issues with data quality and effect of prior bisphosphonate treatment demonstrated that the results of the network meta-analysis were robust to these potential issues.

In the economic evaluation conducted by the assessment group, the incremental cost-effectiveness ratios were found to be > £30,000 per quality-adjusted life-year for all of the non-bisphosphonate treatments (raloxifene, denosumab, teriparatide and romosozumab/alendronate) compared with no treatment across all 10 risk categories when using either QFracture or FRAX to estimate the 10-year absolute risk of fracture. This finding was unchanged when sensitivity analyses were conducted exploring alternative assumptions regarding the duration of persistence with treatment and the duration of time it takes for the treatment effect to fall to zero after treatment stops (the offset period). The results of the regression of incremental net monetary benefit against fracture risk predicted a positive incremental net monetary benefit for denosumab compared with no treatment when valuing a quality-adjusted life-year at £30,000 at very high levels of risk (FRAX score of > 45%), but the estimates of cost-effectiveness are very uncertain at this level of risk. Otherwise, the results of the regression analysis were consistent with the findings based on the 10 risk categories. An exploratory scenario analysis examining an example high-risk patient also suggested that the cost-effectiveness of denosumab may be more favourable among high-risk patients with specific characteristics.

Discussion

Fracture and bone mineral density data were available for all four non-bisphosphonate interventions. All of these interventions were associated with beneficial effects compared with placebo.

One of the strengths of this analysis is that we have been able to estimate the cost-effectiveness of each intervention across the broad range of absolute fracture risk observed in the population eligible for risk assessment under Clinical Guideline 146. However, the downside of the approach we have taken is that the estimates of cost-effectiveness are uncertain for patients at high risk of fracture (e.g. > 30%), as they are informed by fewer simulated patients.

The results of the assessment group's economic evaluation differ from the cost-effectiveness results presented in the submissions by the companies for denosumab and romosozumab. However, the review of cost-effectiveness analyses highlighted a number of important differences between these economic evaluations.

Conclusions

The non-bisphosphonate interventions (raloxifene, denosumab, teriparatide and romosozumab) are all clinically effective at reducing vertebral fracture risk when compared with placebo. However, the effectiveness estimates for other fracture sites are more uncertain and the treatment effects were not statistically significant at a conventional 5% level for all non-bisphosphonate treatments for non-vertebral fractures.

The incremental cost-effectiveness ratios compared with no treatment are above the National Institute for Health and Care Excellence threshold of £20,000 per quality-adjusted life-year for all non-bisphosphonate interventions across the range of QFracture and FRAX scores expected in the population eligible for fracture risk assessment. The incremental cost-effectiveness ratio for denosumab was < £30,000 per quality-adjusted life-year for very high-risk patients (FRAX score of > 45%), based on the regression, but the estimates of cost-effectiveness for high-risk patients are very uncertain.

Study registration:

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