BMJ Open

Use of combination therapy in the treatment of primary osteoporosis: protocol for a network meta-analysis of randomised trials

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To cite: Lou S, Lv H, Chen Y, *et al*. Use of combination therapy in the treatment of primary osteoporosis: protocol for a network meta-analysis of randomised trials. *BMJ Open* 2016;**6**:e012802. doi:10.1136/bmjopen-2016-012802

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-012802).

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Received 25 May 2016
Revised 13 September 2016
Accepted 11 October 2016

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ABSTRACT

Introduction: The existing medications approved for treatment of primary osteoporosis can be divided into antiresorptive drugs and anabolic drugs. According to the mechanisms of action, the combined therapy may produce a synergistic effect on bone mineral density (BMD) compared with monotherapy, and thus improves the efficacy of fracture resistance. This network meta-analysis aims to compare the efficacies of different combined methods for the treatment of primary osteoporosis.

Methods and analysis: MEDLINE, EMBASE and Cochrane databases will be searched to identify all randomised controlled trials (RCTs) and quasi-RCTs that evaluate the effectiveness of combined therapy versus monotherapy for primary osteoporosis. The primary outcome will be the BMD changes at the lumbar spine and total hip, and the secondary outcome will be the risks of vertebral fracture and non-vertebral fracture. The efficacies of different combined methods will be compared via traditional pairwise meta-analysis, trial sequential analysis and Bayesian network meta-analysis. Risk of bias will be assessed using the Cochrane tool and the quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation for network meta-analysis.

Ethics and dissemination: Ethical approval is not required because this is a protocol for a systematic review without including confidential personal data or data on interventions on patients. Our results will be published in a peer-review journal.

Trial registration number: PROSPERO CRD42016038569.

Strengths and limitations of this study

- This is the first systematic review with network meta-analysis aiming to examine which combined therapy intervention is the best for improving bone mineral density in patients of primary osteoporosis.
- Our results will help clinicians to make informed decision about combined therapy of primary osteoporosis, and guide researchers to conduct and report future research on this topic.
- The strengths of this review are the wide search strategy, use of trial sequential analysis to evaluate the power and the necessary sample size, and use of Grading of Recommendations Assessment, Development and Evaluation to evaluate the certainty of evidences.
- A possible limitation is that the results may yield significant heterogeneity that cannot be explained.

INTRODUCTION

Rationale

Osteoporosis is characterised by low bone mass and microarchitectural bone tissue deterioration.[1] Owing to the high mortality and morbidity, osteoporosis-related fractures become a formidable public health threat.[2 3] The annual cost of osteoporosis-related fractures in the USA was estimated to be $16.9 billion in 2005 and predicted to rise to around $25.3 billion by 2025.[4]

Currently, the medications approved for osteoporosis treatment can be mainly divided into two categories: (1) antiresorptive drugs including bisphosphonates,[5] hormone replacement therapy,[6] denosumab,[7] raloxifene[8] and calcitonin,[9] and (2) anabolic drugs such as parathyroid hormone (PTH),[10] peptide PTH (1–34) (teriparatide)[11] and the full-length molecule PTH (1–84).[12] Despite the wide expansion of therapeutic options for osteoporosis over the past two decades, there is still no approved therapy that can fully restore skeletal integrity in most osteoporosis patients. Thus, the options for severe osteoporosis patients remain limited.[13]

Based on the mechanisms of action, there is growing interest in combined therapy of antiresorptive and anabolic drugs in recent years to improve the treatment efficacy. The underlying hypothesis is that combined therapy versus monotherapy may cause an

additive effect on bone formation and bone resorption inhibition, and produce a synergistic effect on bone mineral density (BMD), improving the efficacy of fracture resistance.[14 15] The combination of various anabolic and antiresorptive drugs compared with monotherapy attempts to obtain superior bone mass and strength effects.[13 16–37] However, some studies support the hypothesis[13 17 19 20 22 25] whereas other studies fail to observe significant differences between combined therapy and monotherapy.[23 30–32] To date, the findings are still controversial among studies and the effects of combined therapy are still quite unclear.

Recently, there were three systematic reviews and meta-analyses on combined therapy for the management of primary osteoporosis.[38–40] However, all three studies suffer from one or more of the following limitations: (1) The included articles are not comprehensive;[38–40] (2) Eligible trials do not meet the inclusion criteria;[40] and (3) There is no established hierarchy to determine which combined therapy might be the best for the treatment of primary osteoporosis.[38–40] To the best of our knowledge, there is no network meta-analysis examining the effects of combined therapy on primary osteoporosis.

The purpose of our study is to carry out a network meta-analysis comparing the efficacy of different combined methods for the treatment of primary osteoporosis based on existing randomised controlled trials (RCTs) and ranking these methods for practical consideration. This duration of study was expected to be from May to December 2016.

Objective

The objective of this network meta-analysis of RCTs is to determine if the combined therapy of antiresorptive and anabolic drugs outperforms monotherapy in primary osteoporosis, and determine which combined therapy is best to improve BMD in these patients.

METHODS

Design

This systematic review and NMA protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42016038569). This protocol will be developed following the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).[41]

Eligibility criteria

Participants

Women or men aged ≥45 years old with a high risk of fracture can be included. Both treatment-naïve and treatment-experienced patients will be included. High fracture risk is defined as follows: T score ≤−2.5 at the spine, hip or femoral neck; T score ≤−2.0 with at least one BMD-independent risk factor; or T score ≤−1.0 with history of fragility fracture. Participants with secondary osteoporosis will be excluded.

Interventions

Any combined therapy of anabolic and antiresorptive drugs will be included. The combined therapy is defined as concomitant use of anabolic and antiresorptive drugs. Calcium and vitamin D supplements are considered as adjuncts to drug therapy, rather than antiresorptive drugs.

Comparators

Monotherapy of either antiresorptive or anabolic drugs alone, and antiresorptive or anabolic drugs plus placebo, are defined as the comparator.

Outcomes

The primary outcome will be BMD variation at the lumbar spine and total hip. The secondary outcome will be the risk of vertebral fracture and non-vertebral fracture. The risk of fracture is measured by the occurrence of fractures or by Fracture Risk Assessment Tool (FRAX). BMD is measured by dual energy X-ray absorptiometry (DXA).

Study design

All relevant RCTs and quasi-RCTs will be included. Quasi-RCTs are trials that use the quasi-random method (eg, allocation by date of birth, day of the week, medical record number or month of the year) of allocating participants to different interventions.

Time

Studies of any duration conducted at any time will be included.

Other

Unpublished and published studies written in any language will be included.

Data sources and search

We will systematically search MEDLINE, EMBASE and Cochrane Library from inception to 10 May 2016, with no language restrictions. We also will search ClinicalTrials.gov (http://www.clinicaltrials.gov) and screen the references of both retrieved articles and relative reviews to further identify potentially eligible trials. The searches will be conducted by two authors independently (SL and YC).

Search strategies will be developed using text words as well as Medical Subject Headings (MeSH) associated with terms relevant to osteoporosis, fracture, teriparatide, PTH, together with RCT. As there are diverse antiresorptive drugs, in order to achieve more comprehensive search results, we will ignore the search terms relevant to antiresorptive drugs. The full search strategies used in MEDLINE, EMBASE and Cochrane Library are provided in online supplementary file S1.

Study selection

The search results will be imported into EndNote X7. Two authors (SL and HL) will independently review all titles and abstracts identified from the literature searches and exclude the studies that obviously do not fulfil the inclusion criteria. Then the full texts of the remaining studies will be reviewed to determine whether they meet the inclusion criteria. Any disagreement will be resolved through discussion or be arbitrated by a third reviewer (YC). The process of study selection from databases will be shown in a PRISMA-compliant[42] flow chart (figure 1).

Data extraction

Information will be extracted from all eligible publications carefully and independently by two authors (SL, HL or YC). The data extracted by a single author (SL) will be double-checked by a second author (HL or YC), and discrepancies will be resolved through discussion. The following data will be extracted from each study: first author, year of publication, number of patients, study design, interventions and outcomes. The extracted data will be entered into a standardised Excel file (Microsoft Corporation).

As for missing data in the included trials, we will seek online supplementary appendices or contact the corresponding authors to obtain the missing data and extract the data only presented in figures using digital calipers. We will email the corresponding authors, explaining the study's objective and asking for the original data. We will also inform all the corresponding authors that our paper would appropriately cite and acknowledge their articles. If there is no reply, we will send reminder emails at 2, 4 and 8 weeks after the initial email. If there is still no reply after 12 weeks, we will just perform a descriptive review and summarise the evidences. To minimise inconvenience caused these authors, we will only ask for the data that are necessary for this analysis.

If the original data are not available, we will try to calculate the data through the available coefficients. For example, we will impute the mean from median and SD for SE, IQR, or p value according to the Cochrane Handbook for Systematic Reviews of Interventions.

Outcomes and prioritisation

The primary goal of osteoporosis treatment is to prevent bone fractures. Vertebral fractures are considered as the most prevalent osteoporosis-associated fractures.[43] Hip fractures are most likely to be the international barometer, because of the significant morbidity and mortality.[44] BMD is a key risk factor of fractures,[45] and treatment-induced BMD changes are robustly related with fracture risk reduction.[46–49] BMD variation is an important parameter that evaluates the curative effect of antiosteoporotic drugs.[50 51]

Since vertebral fracture is the most prevalent complication of osteoporosis and hip fracture is the most devastating complication, the primary outcome will be the BMD changes at the lumbar spine and total hip and the secondary outcome will be the risk of vertebral fracture and non-vertebral fracture.

Current guidelines recommend that the long-term use of either antiresorptive drugs or anabolic drugs should be limited to 18–24 months.[52 53] Thus, to more clearly explore the effect of combined therapy, we will divide the results into short-term period (6–12 months) and long-term period (18–24 months).

Risk-of-bias assessment

Two authors (SL and HL) will independently assess the risk of bias. Any disagreement will be resolved through discussion or will be judged by a third reviewer (YC). Risk of bias will be assessed by the Cochrane tool described in the Cochrane Handbook.[54] The following categories are specified: (1) random-sequence generation (selection

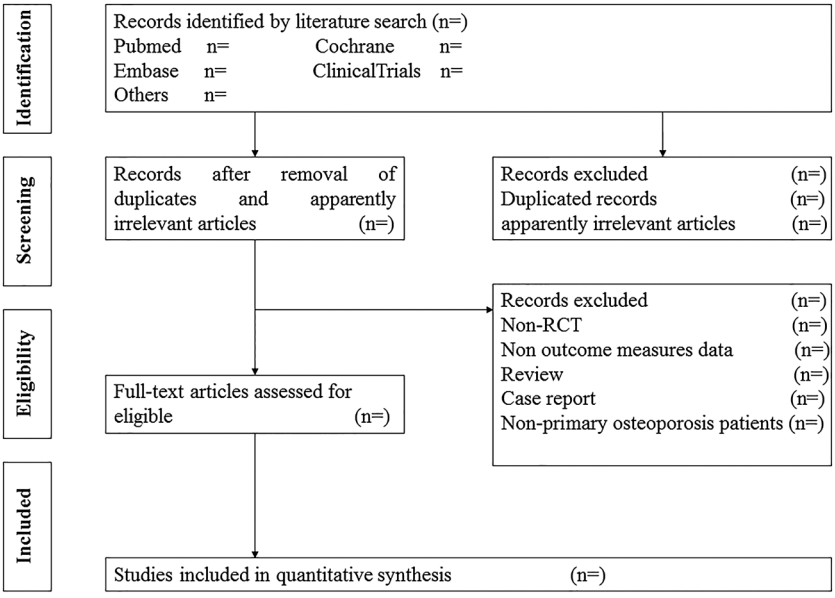

Figure 1 The primary selection process. RCT, randomised controlled trial.

bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); (7) other bias. Each category is divided into three levels: low risk, unclear risk and high risk.

Statistical analysis

Treatments will be directly compared via traditional pairwise meta-analysis on a random effects model, which provides more conservative estimated effects. To assess the heterogeneity of results from individual studies, we will use Cochrane's Q statistic, the I^2 statistic (I^2>50% as a threshold indicating significant heterogeneity) and p values (p<0.10 as a threshold indicating significant heterogeneity).[55] The traditional pairwise meta-analysis will be performed on Review Manager 5.3. Continuous outcomes will be expressed as standardised mean difference (SMD) and 95% CI, while dichotomous outcomes will be expressed as risk ratio (RR) and 95% CI.

Bayesian network meta-analysis will be performed on Markov chain Monte Carlo method in WinBUGS V.1.4.3, and other analyses will be carried out and presented on STATA V.13.0. The fixed and random effects models with vague priors for multiarm trials will be used. The model fit will be measured using the deviance information criterion (DIC), and the model with the lowest DIC will be preferred (difference >3 indicates significant).[56] Dichotomous outcomes will be presented as RR with 95% credibility interval (CrI), while continuous outcomes will be computed by SMD with 95% CrI. The model convergence will be assessed by trace plots and Brooks-Gelman-Rubin plots.[57] After that, the final output will be produced using 50 000 burn-in and 100 000 simulations. Then the node-splitting method will be used to detect the consistency between direct and indirect evidences.[58 59] The probability of each treatment being the most effective will be calculated and graphically ranked with rankograms.[60] The probability will be summarised and reported as the surface under the cumulative ranking area (SUCRA). SUCRAs will be expressed as percentages: 100% for the best treatment and 0% for the worst treatment.[60] If the data are not suitable for synthesis, we will perform a descriptive review and summarise the evidences.

Trial sequential analysis (TSA)

In a meta-analysis, the risk of type I error may be increased due to the random errors because of sparse data and repetitive testing of accumulating data.[61 62] TSA is a method for meta-analysis in order to correct such risk. It provides the necessary sample size for a meta-analysis and determines whether the evidences are reliable and conclusive.[62] In our TSA, we will use one-sided tests, with type I error at 5% and power at 80%. The required information size will be calculated based on a relative risk reduction of 20% in main outcomes. These analyses will be performed on TSA 0.9 β.

Meta-biases

If heterogeneity is detected, the following subgroup analyses will be performed: sex (male or female); duration of treatment (same or different durations); history of treatment (treatment-naïve or treatment-experienced); dose of anabolic drugs (common dose or others); sample size (<50 or ≥50); risk of bias (low risk or high risk).

If enough trials per comparison are included, a sensitivity analysis will be conducted to examine the robustness of our analysis. Furthermore, small-study effects will be assessed using comparison-adjusted funnel plots.[63]

Quality of evidence

Two authors (SL and HL) will independently evaluate the quality of evidence for the primary and secondary outcomes according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) four-step approach for rating the quality of treatment effect estimates from network meta-analysis:[64] (1) present direct and indirect treatment estimates for each comparison of the evidence network; (2) rate the quality of each direct and indirect effect estimate; (3) present the network meta-analysis estimate for each comparison of the evidence network; and (4) rate the quality of each network meta-analysis effect estimate. The quality of evidence will be classified by the GRADE group into four levels: high quality, moderate quality, low quality and very low quality. This process will be performed using GRADE pro V.3.6 software (http://www.gradeworkinggroup.org/).

ETHICS AND DISSEMINATION

Ethical approval is not required given that this is a protocol for a systematic review including no confidential personal data and no data on interventions on patients. The procedures of network meta-analysis will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for network meta-analyses of healthcare interventions,[65] and the results will be submitted to at a professional conference and published in a peer-reviewed journal.

Contributors PT is the guarantor. PT, LZ and SL contributed to the conception and design of this study protocol. SL registered the protocol with the PROSPERO database and edited the draft protocol. The search strategy was developed by SL and YC. SL and HL will screen titles, abstracts and full-text copies of the studies after the literature search. SL, HL or YC will extract information of the included studies after screening. LZ will check the data entry for accuracy and completeness. PT and LZ will give advice for data analysis and presentation of study result. All the authors drafted and critically reviewed this manuscript and approved the final version.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement On completion of this project, all data will be available to anyone who requests such by contacting the corresponding author.

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